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1.	**Your reference**	96.72742
2.	**Patent application number** *(The Patent Office will fill in this part)*	0030929.4
		20DEC00 E592684-1 D00027 P01/7700 0.00-0030929.4
3.	**Full name, address and postcode of the or of each applicant** *(underline all surnames)*	Inverness Medical Limited Beechwood Park North INVERNESS IV2 3ED
		19 DEC 2000
	Patents ADP number *(if you know it)*	7849847001
	If the applicant is a corporate body, give country/state of incorporation	United Kingdom
4.	**Title of the invention**	Analyte Measurement
5.	**Name of your agent** *(if you have one)*	Frank B. Dehn & Co.
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	179 Queen Victoria Street London EC4V 4EL
	Patents ADP number *(if you know it)*	166001

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7.	**If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application**	**Number of earlier application**	**Date of filing** *(day / month / year)*

8.	**Is a statement of inventorship and of right to grant of a patent required in support of this request?** *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	Yes

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12. Name and daytime telephone number of person to contact in the United Kingdom

Adrian Samuels
01273 244200

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Analyte Measurement

This invention relates to apparatus for and methods of measuring certain properties of a fluid particularly although not exclusively, bodily fluids and the concentrations of certain analytes therein. At least some aspects of the invention relate particularly to the measurement of glucose levels in blood and other body fluids such as cutaneous (interstitial) and sub-cutaneous fluid.

Over recent years there have been two obvious trends in diagnostic device development: simplification of the test procedure and reduction in the volume of sample required to perform the test. Test simplification allows the assay to be performed by relatively untrained personnel in a "non-laboratory" setting. Thus, for example, cardiac marker tests configured in a lateral flow immunoassay format with labelled antibody allow for early assessment of potential myocardial infarct.

The driving force for the development of tests requiring smaller sample volumes is the reduction of discomfort of the patient. This is particularly important in home tests where, for example, if a glucose test is less painful the user will test more frequently. It is now well documented that diabetics who monitor their blood sugar frequently achieve better glycaemic control and so avoid long-term complications of the disease. With this thought in mind, a number of companies have developed test devices requiring progressively smaller sample volumes, thereby minimising pain.

Some proposals have been made to attempt to reduce the amount of pain involved by with so-called minimally invasive devices (e.g. Integ US patent numbers

5,746,217; 5,820,570; and 5,582,184). Unfortunately, such devices appear to be unable to provide sufficient fluid sample to provide a reliable result and thus, as yet, none has been commercially realised.

In the context of glucose measurement, so-called continuous monitors are also known and these have certain advantages over the 'snapshot' devices outlined above since they provide a clearer insight into trending, the effect of food or medication and overall glycaemic control. Such known devices however suffer from a number of drawbacks, mainly associated with the need to recalibrate the device regularly. This entails performing regular manual tests using a conventional test strip. This can negate many of the advantages of using a continuous device since the user is still relied upon to take action in order for the device to operate properly. Furthermore the accuracy of the devices tends to drift unpredictably between calibrations. The regular finger pricks are also painful.

It is an object of the invention to provide an improved arrangement and when viewed from a first aspect the invention provides a device for measuring the concentration of an analyte in a fluid, comprising a support member, analyte sensing means provided thereon for measuring said concentration and a microchannel in fluid communication with said analyte sensing means for conveying said fluid to said sensing means.

Thus it will be seen that in accordance with the invention a microchannel is used to convey the sample fluid to the sensing means.

As used herein the term "microchannel" refers to a channel, of any suitable cross-section, whose smallest lateral dimension is less than approximately 500 μm. In the microchannels of the preferred embodiments of the invention this dimension is preferably less than 200 μm, most preferably between 10-200 μm. The length of such channels is preferably less than 10mm, thus giving an

overall preferred volume of less than 200 nanolitres

Such microchannels are beneficial for a number of reasons in the context of an analyte sensing device. Most importantly the volume of fluid required to carry out an assay is correspondingly small. In the context of the measurement of a bodily fluid a small sample volume is beneficial since it means that it is easier to provide a sufficient volume for a valid test. Especially in the context of blood or interstitial fluid measurement, a reduction in sample volume can also corresponds to a reduction in pain since e.g. a smaller needle can be used.

The analyte sensing means can be arranged in any suitable configuration depending on the type of sensing means used (electrochemical, optochemical etc.). Preferably the analyte sensing means comprises one or more reagents to react with said analyte and thereby give a measurable output. Such a reagent may be located anywhere, but preferably the reagent or at least one of the reagents is provided on a wall of the microchannel. This arrangement is beneficial since it means that no additional volume is required in order for the sample liquid to be brought fully into contact with the reagent - i.e. the contact area is optimised. Moreover the thickness of the layer of reagent can help to reduce the volume of the microchannel even further.

This is considered to be novel and inventive in its own right and thus when viewed from a second aspect the invention provides a device for measuring the concentration of an analyte in a fluid, comprising a support member and a microchannel provided on said support member for conveying said fluid across the support member, wherein one or more reagents for reacting with said analyte is coated on a wall of the microchannel.

Preferably such a device further comprises means for sensing the analyte - i.e. means for measuring the

output of the reaction between the analyte and the reagent.

The devices set out hereinabove may be used for measuring any suitable analyte in any suitable fluid. However the invention, in its various aspects, finds particularly beneficial application in the measurement of analytes in human or animal bodily fluids. Of course, a suitable sample of bodily fluid may be applied to the device. Preferably however the device is integrated with means for extracting the fluid. Most preferably this comprises means for penetrating the skin - in the case where the sample fluid is blood or interstitial fluid. Most preferably it comprises a skin penetration member such as hollow needle, solid lance or the like.

In accordance with the embodiments set out above the device can be used both to collect the sample fluid and to measure the concentration of the target analyte - or at least give an output from which the concentration can be measured. This is considered to be novel and inventive in its own right and thus when viewed from a third aspect the present invention provides a device for measuring the concentration of an analyte in a fluid, comprising a support member, means provided on the support member for sensing said analyte, wherein said support member further comprises fluid extraction means arranged to direct fluid to said analyte sensing means via a conduit on the support member.

Thus it will be seen that in accordance with this aspect of the invention a fluid extraction means, preferably a skin penetration means, most preferably a needle, lance or the like, is provided on a support member of a device for measuring analyte concentration. This allows, in at least preferred embodiments, the combination of skin penetration means, e.g. needle, and support member, e.g. test strip, to be made disposable and thus as hygienic as possible. It will be

appreciated that this concept is a significant departure from prior art arrangements in which, for example, a user would have to pierce their skin using a lance, and thereafter apply the resulting drop of blood to a test strip which is then inserted into a test meter. Instead in such applications the step of transferring a drop of blood to a test strip could, in accordance with the present invention, be avoided. Instead preferred embodiments require a user merely to puncture their skin with a needle or the like and then blood or interstitial fluid may be conducted onto the test member.

In such embodiments the combined needle/test member would normally be used in conjunction with a separate, non-disposable, measuring device for measuring the analyte concentration e.g. by means of the output of an analyte-reagent reaction, where appropriate.

The dimensions of the needle, lance or the like may be suited to the particular application. For example a standard hyperdermic needle several centimetres in length may be employed. In preferred embodiments however, the penetration member is of such a length that it penetrates only the cutaneous layer of skin, not the sub-cutaneous layer.

Such devices are particularly advantageous. By penetrating only the cutaneous layer, interstitial fluid may be extracted. The cutaneous layer has a high density of blood capillaries which helps to ensure that the levels of analytes in interstitial fluid reliably reflect those in the blood. Furthermore interstitial fluid is abundantly available from almost any skin surface and has a relatively low viscosity.

A further benefit offered by interstitial fluid is that it is much simpler than whole blood and therefore does not, for example, suffer from Haematocrit fluctuations, and its simplicity makes the use of reagentless tests, such as infra-red spectroscopy, filter photometry or Kromoscopy, more feasible.

Perhaps more importantly such shallow skin penetration substantially reduces the pain experienced since there is a much lower density of nerve endings than at the depths penetrated by standard needles when extracting blood. Indeed, in at least preferred embodiments, no pain is normally felt. This makes prolonged and/or repeated penetration of the skin much more acceptable.

The actual length of the penetration means will depend on the angle at which it is intended to be inserted. Thus if shallow angle penetration is intended, the length may by of the order of several millimetres e.g up to approximately 7 to 10 millimetres. Preferably however substantially perpendicular insertion is intended and the length is less than 2 mm, preferably less than 1.5 mm. In some preferred embodiments a length of approximately 1.4 mm is appropriate. However for certain applications a length as short as 0.5mm may be preferred.

Of course a given test member may have just one skin penetration member, or alternatively a plurality may be provided.

The test member may be of any suitable type or configuration. Preferably it comprises a microchannel and analyte sensing means as set out earlier. This combination has particular benefits since it can give a device which is painless or at least substantially less painful than known devices presently used, with the microchannel ensuring that the small sample volume delivered by the small penetration member is sufficient to give a reliable result. The low sample volume requirement of a microchannel also allows the device reliably to use interstitial fluid, the benefits of which are given above.

It will be seen therefore that such a combination is novel and inventive in its own right and when viewed from a further aspect the present invention provides a

device for measuring the concentration of an analyte in a bodily fluid, comprising skin penetration means, said penetration means being sufficiently short so as to penetrate only the cutaneous layer of skin without penetrating the sub-cutaneous layer, and a support member, said support member comprising an analyte sensing site and a microchannel for conducting said bodily fluid from said penetration member to said analyte sensing site.

The penetration means may comprise a sufficiently short standard needle, possibly shortened if necessary. More preferably the penetration means comprises a microneedle. A microneedle is hereby defined as a needle with a length sufficient to penetrate the cutaneuous layer of human skin without penetrating the sub-cutaneous layer. Preferably a microneedle will penetrate the epidermis, but not the dermis. Such a needle typically has length less than 2mm, preferably between 0.4 and 1.6mm.

The outer diameter is preferably less than 0.5mm, most peferably between 0.1 and 0.3 mm.

The penetration means need not be integrated with the support member, but preferably is. The comments above regarding this arrangement apply, with the additional benefit noted here that preferred embodiments of this arrangement can provide a compact disposable device which gives rise to substantially no pain, in use and obviates the need for a user to come into contact with or even see the bodily fluid concerned.

Where devices in accordance with the previous aspects of the invention set out hereinabove may be used to measure any suitable fluid, this is preferably a bodily fluid. If a bodily fluid is measured, this could, for example, be blood, urine etc. However for the reasons set out above, preferred embodiments of any such aspects of the invention are arranged to measure the concentration of an analyte in interstitial fluid.

The analyte being measured will generally depend on the fluid being measured. In a particularly preferred embodiment the analyte is glucose. This is clearly an extremely important measurement in the context of those suffering from diabetes, particularly where, in accordance with the preferred arrangements set out above, the pain experienced in taking a measurement can be reduced, since such measurements need to be taken regularly and frequently.

Whilst the concentration of glucose in blood may be measured directly, advantageously embodiments of the invention allow it to be measured in interstitial fluid. As mentioned before this can give painless, reliable results when a microneedle is used in association with a microchannel on the test member. It should be appreciated therefore that the aforementioned combination is considered especially advantageous.

Except where the contrary is stated, the required analyte may be measured in accordance with the various aspects of the invention set out in any suitable way, which will, in general, depend upon the analyte being sensed. For example a reagentless measurement technique such as infra-red radiation measurement may be used.

Preferred embodiments of the invention however use a reagent-based measurement. Many different reagent-based analyte measurements are available to those skilled in the art, allowing the principles of the invention to find wide application. For example an optochemical- i.e either fluorescent or luminescent - or an electrochemical technique could be used.

One preferred embodiment comprises analyte sensing means comprising a mediated amperometric enzyme electrode. For example, a ferrocene-mediated electron transfer from a glucose-oxidase catalysed reaction is a suitable means for detecting the level of glucose in a body fluid. Other enzymes, such as lactate oxidase or lactate dehydrogenase and cholesterol oxidase

dehydrogenase may be used to measure lactate and cholesterol levels respectively. Other suitable electron-transfer mediators include components of the respiratory chain (i.e. cytochromes).

It should also be understood that detection means such as electrochemical ELISA (enzyme-linked immunosorbent assay) can be used.

Devices in accordance with the invention could comprises just one means for sensing an analyte. For example a disposable test member with integral skin penetration member is a particularly preferred embodiment which offers significant benefits over traditional test strips such as those used for measuring blood glucose, such as obviating the need for a user to come into contact with or even see their blood and also the need to transfer blood onto a test strip.

Typically such an embodiment will comprise an analyte sensing means which operates in conjunction with a test meter to give the measurement. For example the test member may comprise suitable electrochemical electrodes to which contacts in the test meter make electrical connection. Alternatively the member may comprise the appropriate reagent or dye for performing a colorimetric test in association with light sensitive means in the test meter. It will be seen that such arrangements are consistent with the test device being disposable since the costly elements of the sensing mechanism, such as the light sensitive means, electronic circuity etc., can be placed in a non-disposable test meter. Potentially therefore such a test device may be used like a conventional test strip but without the user having separately to prick their finger to produce a drop of blood to put onto a strip.

Just single analyte sensing means may be provided, but preferably more than one is provided. This arrangement is novel and inventive in its own right and thus when viewed from a further aspect the invention

provides a device for measuring the concentration of an analyte in a fluid, comprising a support member and a plurality of analyte sensing means provided thereon for measuring said concentration, wherein said device further comprises a plurality of conduits such that each of said sensing means has a conduit associated therewith, said conduits serving in use to direct said fluid to respective sensing means.

Thus it will be seen that in accordance with this aspect of the invention, a plurality of conduits direct fluid to be measured to respective analyte sensing means. This means that a plurality of measurements of fluid may be made by a single such device. The sensing means may be different so as to measure or test for different analytes in the fluid. Preferably however they are the same or at least are for measuring the same analyte.

As described above, the sensing means may be electrochemical or non-electrochemical in nature - e.g. of the fluorescent or chemi-luminescent colorimetric sort. For example the sensing means may comprises an enzyme-coated electrode in the case of electrochemical measurement, or in the case of fluorescent colorimetric sensing the sensing means would comprise a suitable reagent dye. It will, of course, be understood that the term 'sensing means' does not necessarily refer to a complete assembly for giving a final reading, but rather to a means on the support member which yields an output which may be read to give a measure of the analyte concentration, e.g. by a separate test meter.

Such devices as are described in the aspect of the invention set out above could be arranged to be used in a mode similar to conventional test strips i.e. where a single fluid sample is placed on the device and is measured. Used in this way a plurality of measurements of the sample may be made and for example the average taken to give a highly precise measurement.

Preferably however the device is arranged to remain in communication with the test fluid for a prolonged period -i.e. longer than is necessary to perform a single test. This allows the plurality of sensing means to take measurements of the fluid at different times and therefore monitor the concentration of the analyte in the fluid over a period of time.

In common with earlier aspects of the invention, devices of the sort set out above may be arranged to measure the concentration of any suitable analyte. In all such cases, the analyte's concentration may simply be an indirect indication of the property of the sample fluid which it is desired to monitor. For example a detection reagent (e.g. an enzyme substrate or an antigen) may be added to the sample so as to bind selectively and/or react with certain proteins in the fluid such as enzymes or antibodies. In this case the added detection reagent or the product of the enzyme-catalysed reaction, comprises the analyte. Devices in accordance with the invention can therefore be arranged to measure such analytes - i.e. it will be seen that such devices may be used to measure the activity of enzymes in a body fluid sample, or test whether antibodies to a particular antigen are present in the body fluid.

Preferably however, the device is arranged to measure an analyte concentration directly - i.e. it is the concentration itself which is being monitored. An example of such a measurement would be glucose in blood, the concentration of which is an important parameter for those suffering from diabetes.

In a particularly preferred embodiment the measuring device is suitable for measuring the concentration of an analyte, e.g. glucose, in blood or interstitial fluid. In such an embodiment the device is preferably suitable for attachment to the skin of the subject who is to be measured. The subject may be an

animal but is preferably human.

It will be seen therefore that a preferred embodiment of the invention provides a measuring device of the kind set out hereinabove for attachment to a subject and for measuring the concentration of an analyte in blood or interstitial fluid, preferably comprising means for attaching the device to the skin of the subject. By providing a device which can be attached to a subject, measurements of the concentration of the substance in the subject's blood or interstitial fluid can be carried out repeatedly over a period of time without the subject having to provide a blood sample which is applied to a conventional test strip.

This means that inconvenience and discomfort to the user is significantly reduced and moreover that tests can be carried out at regular intervals and at a greater frequency than would otherwise be tolerable. The result of this in the preferred application of the invention to blood glucose monitoring is that an improved insight into glycaemic control and the effects of food, medication and general trends on the glucose level is given.

It is mentioned above that in preferred embodiments, the sample fluid in question is blood or interstitial fluid. At least where it is glucose which is the analyte in question, interstitial fluid is preferred of these. The reasons for this are set earlier and apply equally to the presently described devices. In particular the minimal skin penetration necessary to extract interstitial fluid reduces pain.

Accordingly it is preferred that the devices comprise a penetration member sufficiently short only to penetrate the cutaneous layer of skin, most preferably integral formed. It is further preferred that such devices comprises at least one microchannel for conveying the interstitial fluid to one or more of the sensing meanss.

It will be appreciated that the types of devices set out above are both novel and inventive in their own right and thus when viewed from a further aspect the present invention provides a device for measuring the concentration of a given analyte in a bodily fluid comprising means for attaching the device to the skin of a subject and a plurality of sensing means for making a plurality of measurements of said concentration over a period of time.

It will be seen that effectively this aspect of the invention provides a device which can perform a plurality of measurements *in situ*, that is without user intervention being required. This has clear benefits in removing some constraints on the number, frequency and regularity with which measurements can be performed. In this regard the device gives many of the benefits of a continuous sensor but without necessarily the drawbacks associated with truly continuous sensors which require frequent recalibration, since each sensing means can effectively be of the single-use type used in conventional test strips and which does not need separate calibration.

Preferably the device has one or more of the preferred features set out earlier in the context of previous aspects of the invention. Furthermore the device is preferably arranged to take measurements at predetermined intervals. Preferably this is achieved, by providing the device with flow control means for influencing the flow of fluid to the sensing means. Any suitable flow control method may be employed with corresponding means to effect such a control method. For example Piezo-electric pumping, electrophoresis or mechanical methods such as 'unblocking' the flow along a selected conduit - e.g. by allowing a gas bubble to escape or by opening a valve.

In preferred embodiments the flow control means

comprises a hydrophobic gate which comprises a surface of the conduit / microchannel etc. In one possible embodiment the hydrophobic nature of the gate may be reduced changed in use selectively to promote an aqueous fluid to flow along the channel. For example, a hydrophilic base material covered by the hydrophobic material could be exposed by heating or electrodesorption, or the hypdrophobic layer itself could be elctro-oxidised in order to make it more hydrophilic.

Prefereably however, the hydrophobic gate may be maintained as it is and a increased pumping force (e.g. provided by a mechanical or electro-osmotic pump) may be applied in order for the fluid to breach the hydrophobic gate.

Preferably the device is arranged to direct fluid sequentially to each of the sensing means. The timing of the direction of the fluid to the sensing means could be pre-configured e.g. resulting from the physical arrangement of the sensing means. Preferably however the device comprises, or is adapted to interface with, control means generating signals to control said direction of the fluid to the sensing means. Such control is preferably automatic i.e. the pattern of signals for directing fluid to the respective sensing meanss is predetermined, most preferably a regular series of signals.

Additionally or alternatively however the control means may be such as to allow a user to specify when a measurement is to be made. This is beneficial as it allows measurement on demand which is useful for example in the case of blood glucose monitoring, as it allows the user to determine the effect on blood glucose of eating a particular snack or to determine how much insulin it is necessary to inject prior to eating or the user may simply want to carry out a check for reassurance. This enables the device to make periodic

measurements of fluid from the body of the subject using fresh fluid for each measurement, thereby facilitating the desired object of monitoring the concentration of the substance in question over a period of time.

Where, as is preferred, each microchannel or other conduit is associated with a respective flow control means, each may be individually addressable by a suitable control means. This gives significant flexibility in how such a device may be used.

In common with earlier arrangements, any suitable method of transduction, e.g infra-red or electrochemical, may be employed. However, an array of individually addressable channels and associated sensing meanss is especially useful with colorimetric transduction methods, particularly where these involve the irreversible generation of dye. The reason for this is that each channel and sensing means may be treated as 'single use'.

Preferably the device comprises a common fluid collection region in fluid communication with the bodily fluid to be measured - e.g. via a needle - each sensing means preferably being in selective fluid communication with said common collection region. Such an arrangement is considered to be novel and inventive in its own right and thus when viewed from a further aspect the present invention provides a device for making a plurality of measurements of the concentration of an analyte in a fluid comprising a common sample collection site in fluid communication with the fluid to be measured and a plurality of sensing means for measuring said concentration.

It will be appreciated by those skilled in the art that arrangements in accordance with at least preferred embodiments of the invention set out above provide a device for repeatedly measuring the concentration of at least one analyte in a fluid. Such arrangements are beneficial for various reasons as set out already

herein. However the Applicants have realised that such repeated measurements are particularly advantageous when used in conjunction with a continuous sensor since they can be used to perform the periodic recalibration measurements which are generally needed.

Thus in a particularly preferred embodiment the device comprises a sensing means for making a substantially continuous measurement of the concentration said substance. This embodiment gives all the benefits of a continuous sensor as set out hereinbefore but without the disadvantages associated with having to perform manual tests to recalibrate. Furthermore the arrangement gives an additional advantage, at least in preferred forms, that the calibration tests can be carried out using exactly the same fluid as is measured by the continuous sensing means thereby obviating the need to assume that there is uniformity between two samples of fluid as is the case with present manual calibration tests.

It will be seen that a measuring device including a continuous sensing means and at least one calibration sensing means is novel and inventive in its own right and thus when viewed from a yet further aspect the present invention provides a device for measuring the concentration of an analyte in a fluid comprising a sensing means for measuring said concentration substantially continuously and calibration sensing means for performing at least one calibration measurement.

The calibration sensing means preferably comprises a plurality of individual sensing meanss to allow a series of periodic calibration measurements to be performed.

Preferably the continuous sensing means and calibration sensing means(s) are provided on a common base member, most preferably a patch or the like for attachment to the skin of a user. This arrangement realises the benefits mentioned before associated with

locating the sensing meanss together and thus obviating the need for user intervention in performing calibration of the continuous sensing means. Thus, for example, previous problems associated with transferring a sample to a measuring device are obviated. Similarly in applications where a blood analyte such as glucose is being monitored there need no longer be a requirement for a user to prick themselves in order to provide a blood sample for calibration purposes, since calibration can effectively be carried out *in situ*.

In addition to the preferred features set out above, the preferred features of the earlier aspects of the invention are, where applicable, preferred features of the present aspect. Thus for example flow control means are preferably provided, at least associated with fluid conduits for conducting fluid to the calibration sensing means. Most preferably the flow control means comprises an electro-osmotic pumping arrangement. Similarly the device is preferably suitable for attachment to a user's skin.

The calibration sensing means is preferably of the single use type - i.e. which can only be used to perform a single measurement. This is advantageous as such sensors are generally more accurate than continuous ones, which cannot be factory calibrated and tend to suffer from electrode fouling as a result of continuous contact with bodily fluid.

The calibration sensing means may be up or downstream of the continuous sensing means but is preferably downstream since the continuous sensing means will generally not use up the substance being measured whereas the calibration sensing means(s) will, especially if it/they are of the single use type.

Where not otherwise specified, any suitable conduit may be provided for conveying the fluid to be measured to the sensing means, depending upon the flow control means where provided, but preferred arrangements

comprise microchannels as defined herein.

As was explained above, such microchannels are beneficial for a number of reasons. Furthermore in the context of a plurality of analyte sensing means, the provision of microchannels allows many test elements to be positioned in close proximity thereby enabling even devices comprising a large number of sensing meanss to be made relatively small. This is beneficial in applications where the device is intended to be worn by a user - e.g. by being attached to the user's skin - since it makes the device more comfortable.

Also, where electrochemical ELISA detection means are employed, the diffusional restriction that occurs in the microchannel can enhance the results obtained from such detection methods, as the electro-active species are generated in close proximity to the electrode.

As well as the understood benefits *per se* of a low sample volume arising from the use of microchannels, the Applicants have realised that such a small sample volume makes it practicable to change the mode of testing. More particularly it has been realised that a very low sample volume means that rather than conduct the usual reaction rate measurement as in known electrochemical devices e.g. for detecting blood analytes such as glucose, where electron transfer is measured as a function of time to determine the rate of transfer, an end-point test can be carried out in which the total amount of analyte in the sample volume is measured, thereby consuming substantially all of the analyte.

It has been appreciated that this is advantageous over rate measurements since the latter tend to be prone to interference, temperature and Haematocrit fluctuations. Whereas such a measurement method would take a prohibitively long time with known measuring devices, by using microchannels in accordance with the invention to give a required sample volume of the order of a few nano-litres, such a measurement can typically

be completed in the order of a few seconds, thereby making it a practical proposition.

It will be appreciated that this method is novel and inventive in its own right and thus when viewed from a yet further aspect the present invention provides a method of measuring the amount of an analyte in a sample of liquid comprising providing an electrochemical measuring device having a sensor electrode within a microchannel, introducing said sample liquid into said microchannel, and measuring an aggregate current passed by said electrode to give an indication of said amount of analyte in the sample.

This aspect of the invention also extends to an electrochemical device for measuring the amount of an analyte in a sample of liquid comprising a sensor electrode disposed within a microchannel and means for measuring an aggregate current passed by said electrode in use to give an indication of said amount of analyte in the sample.

The invention also extends to an equivalent arrangement using a non-electrochemical sensing means - e.g. a colorimetric one.

Where a continuous sensing means is used, as is discussed earlier, a further advantage of the use of microchannels to convey the sample fluid thereto is that a continuous flow over the sensing means is facilitated.

It will be appreciated by those skilled in the art that a test element comprising a microchannel for conveying fluid to a sensing means is novel and inventive in its own right and thus when viewed from a further broad aspect the present invention provides a test element comprising a microchannel for conveying a test fluid to an electrochemical sensing means.

As will have been seen from the foregoing description either a feature or a preferred feature of the various aspects of the invention set out is that a measuring device be suitable for attachment to a user's

skin in order, for example, to be able to measure the concentration of an analyte in a bodily fluid. In accordance with such embodiments therefore it is preferred that the measuring device comprises transfer means for transferring said bodily fluid from the user's body to the sensitive part of the device. Where, as is preferred, the device comprises a conduit, most preferably a microchannel, for conveying the fluid to the sensing means thereof, the transfer means is preferably arranged to transfer the fluid to the upstream end of the conduit.

The transfer means may employ any suitable means for transferring the fluid from the user's body. Preferably a semi-invasive method is used such as suction, ultra-sound or iontophoresis. Other alternatives include so-called hole fibres and capillaries which are used in a variety of chromatographic techniques.

More preferably however the transfer means comprises a needle. In particularly preferred embodiments the needle is a microneedle as defined hereinabove, i.e. of such a length that it penetrates the cutaneous layer of skin, but not the sub-cutaneous layer etc.

The needle is preferably shaped to aid skin penetration. For example the tip region of the needle is preferably substantially conical. Furthermore it is preferred that the tip region has a reduced cross-section - preferably less than 0.2mm in width, most preferably less than 0.05mm in width.

Moreover the needle is preferably arranged to minimise the risk of blockage upon insertion into skin. For example the aperture of the needle may be provided on a side surface of the needle, rather than at the tip as is conventional. Preferably the aperture of the needle is recessed, thereby avoiding contact with the skin upon penetration and thus potential blocking and/or

damage

The needle preferably has a bore such that the sample fluid is drawn up by capillary action e.g. approximately 29 gauge.

Most preferably one or more microneedles is employed as defined hereinabove.

Examples of etched microneedles are given in US 5855801 and US 5928207. Alternatively such microneedles may be formed by electroplating or micro-injection moulding. The latter two methods are preferred for mass production as they are more cost efficient.

The methods above may be supplemented by applying pressure to the user's skin around the site at which it is penetrated. Such pressure could be applied purely manually, but preferably the device comprises means - e.g. suitably configured resilient means - to apply the pressure.

These principles apply equally to other aspects and embodiments of the present which require a bodily fluid to be transferred from the user's body onto a measuring device.

Embodiments of the aspects of the invention set out hereinabove can advantageously be used to monitor the levels of blood analytes such as glucose. This may be done periodically in accordance with some embodiments, or continuously in accordance with other embodiments. Knowledge of, say, blood glucose level is clearly useful for diabetics who can use this information to decide when and how much insulin to self-administer.

Preferably therefore the devices of the preferred embodiments comprise display means to display the concentration of the analyte being measured such as blood glucose. Such display means may be coupled directly to the measuring device, but preferably it is separate from the device and receives data therefrom by telemetry. This approach has the advantage that the measuring device can be very light and thus comfortable

to wear. For example the measuring device may be worn under clothing but monitored on a display means kept, say, in a pocket, without the user having to disturb their clothing in order to view it.

Additionally or alternatively the device comprises or is coupled to means for administering a substance to a user on the device on the basis of the measured concentration. Thus in the previous example of a blood glucose monitoring device, rather than just being a passive monitoring device, undoubtedly useful *per se*, such a device can be used in conjunction with an insulin pump to maintain the user's glucose level within a desired range. The benefits of such an arrangement are clear and are facilitated, at least in part, in accordance with preferred embodiments of the invention by the plurality of sensing means, preferably provided on a member suitable for attachment to a user's skin, which enable frequent periodic tests or periodic recalibrations of a continuous sensor.

By effectively providing a feedback loop, preferred embodiments of this inventive feature can allow say a diabetic, to maintain control of his/her glucose levels with having to carry out any self-testing at all i.e. with only intervention to replace consumable items such as a sensor/insulin patch being necessary.

Furthermore, particularly where a continuous sensing means is employed, tighter control of, say glucose level, is achievable than where intermittent manual tests and insulin administration are used.

Such an arrangement is therefore considered to be novel and inventive in its own right and thus when viewed from a yet further aspect the present invention provides an apparatus for administering a substance to a user comprising a measuring device for measuring the concentration of an analyte in a bodily fluid from said user, said measuring device comprising a plurality of analyte sensing means and at least one conduit,

preferably a microchannel, for conveying said bodily fluid to at least one of the sensing means; the apparatus further comprising means to administer said substance to said user on the basis of said measurement of concentration.

In accordance with all appropriate aspects of the invention, the measuring device preferably comprises a self-adhesive patch for attachment to the skin of a user. This can provide a secure but comfortable arrangement for use over prolonged periods of time, and can be relatively unobtrusive.

The means for administering the substance may be entirely separate from the measuring device. At least in some preferred embodiments however it is integrated therewith. Preferably such an integrated administering means comprises a reservoir on or in the measuring device for dispensing the substance. In a particular embodiment the substance, such as insulin, is contained within a reservoir on an adhesive patch. The actual means for getting the substance from such a reservoir could comprises anything suitable such as a pressurised supply in conjunction with a flow control means such as a valve. Preferably however a pump is used. In a preferred embodiment a single pump may be used both to administer the substance, such as insulin, to a user's body and also to draw out blood or preferably interstitial fluid, to a sensing means for making an analyte concentration measurement e.g. of glucose.

Thus, for example, a suitable device may comprise an adhesive patch comprising a microneedle (as defined herein) coupled to or in fluid communication with an array of microchannels and a separate needle for injecting insulin. In a preferred embodiment a single pump, e.g. a silicon micro-pump, may be used to inject insulin from a reservoir on the patch and to draw interstitial fluid over a glucose sensing means to a waste reservoir.

Where an embodiment of the invention calls for control and/or data processing means, these will generally comprise electronic means such as an integrated circuit or the like. A power supply is then also required. Preferably such control/processing means are portable. It or they may be provided in an integral package with the device e.g. the adhesive patch. Alternatively the control/processing means and/or power source may be provided separately and communicate with measuring device via a wire or wireless telemetry link as mentioned above.

The power source may be a battery or may be a 'renewable' source such as a solar cell or a dynamo energised by movement of the user. Of course a combination of these could be employed.

Measuring devices in accordance with the present invention may be fabricated using any suitable technique. In particular, where provided, the microchannels may be made using any suitable micro-fabrication technique such as embossing, plasma etching or laser photo-ablation.

In one preferred embodiment, electrodes are provided on opposing sides of a fluid channel by forming a first channel which is filled with a conductive material, and forming a second channel for conveying the test fluid, the second channel cutting across the first thereby to form electrodes within respective opposite sides of the second channel.

This technique is believed to be novel and inventive in its own right and thus when viewed from another aspect the present invention provides a method of making a device for measuring the concentration of a substance in a liquid comprising forming a first channel in a substrate material, fitting said channel at least partially with an electrically conductive material, and forming a second channel so as to intersect said first channel, thereby forming two conductive portions on

respective opposite sides of the second channel.

The conductive portions formed in accordance with the invention could be utilised for any convenient purpose. For example one or both could comprise an electrode for an electrochemical sensor arrangement and/or one or both could be used as part of an electro-osmotic pumping arrangement.

Micromachining techniques are preferred since they can be used to fabricate microchannels as defined herein which can therefore be formed close to one another, permitting dense arrays thereof. Furthermore, where the device has flow control means operating via electro-osmotic force, the driving electrodes are preferably positioned in close proximity to one another. This allows high electric fields to be achieved without applying unnecessarily high voltages. Preferably such driving electrodes are provided substantially on one side of a channel. In one preferred embodiment the driving electrodes extend circumferentially around an arcuate wall of the channel.

As mentioned above, the technique set out in the present aspect of the invention is a preferred one for fabricating devices in accordance with earlier aspects of the invention. Alternatively such devices may be made by forming suitable areas of conducting material with a substrate e.g. areas of carbon loaded plastic within a plastic substrate.

In a preferred variant of the method above, one or more electrodes may be formed on a second substrate which is then laminated to the main support member of the device. This technique could be used on its own to provide electrodes or in combination with another such as the previous one. This latter possibility makes it easier to provide different electrodes for different purposes. For example in a preferred embodiment, carbon electrodes (coated with an enzyme) are provided on opposing walls of the channel, using the first

technique, for an electrochemical sensor and two gold electrodes are provided adjacent one another on a substrate laminated onto the support member for an electro-osmotic pump.

If a second substrate is provided, preferably it is arranged to close the channel provided on the support member. This allows a very straightforward fabrication method in which a single support member may be machined, preferably with at least one integral needle, to form an open channel, preferably a microchannel, which channel is then covered by a layer laminated thereon.

This is considered to be novel and inventive in its own right and thus when viewed from a yet further aspect the present invention provides a method of fabricating a device for measuring the concentration of an analyte in a fluid comprising providing a support member, forming an open channel on a surface of the support member and laminating a second layer onto said support member so as to close said channel.

The invention also extends to a device fabricated using such a method.

It will be understood that it is preferred in accordance with this aspect of the invention that the channel is a microchannel, and/or that an integral needle is formed, as is mentioned above. In one particularly preferred embodiment an integrated skin penetration member is provided which is also open on one side. This could also be covered by the laminated second layer to form a hollow needle for extracting fluid. However not only would this require the needle to be substantially coplanar with the upper surface of the support member, but it would require a narrow elongation of the second layer which would have to be accurately aligned with the formed penetration member.

More preferably therefore the penetration member is arranged so that upon insertion into skin, the skin itself effectively forms a wall of the member to that it

can act like a hollow needle. Most preferably this is achieved by forming the penetration member with walls tapering away from the open side - e.g. a V shape.

This concept, too, is novel and inventive in its own right and thus when viewed from a further aspect the invention provides an apparatus for obtaining fluid through human or animal skin, comprising a skin penetration member having at least one longitudinal side open, the other sides being arranged so as effectively to cause the penetrated skin to act as the remaining longitudinal side of the member when the penetration member is inserted into the skin.

It will be seen by those skilled in the art that such a penetration member may be easily formed e.g. by machining a monolithic element or by injection moulding. By contrast it is significantly more difficult to fabricate, e.g. by injection moulding, a hollow needle, particularly one with dimensions of the order of fractions of a millimetre as are preferred in accordance with the present invention.

Where an optical measurement technique is employed, the result may be such that a user can determine it with the naked eye. However a light sensing means will, in general, be required. In some cases a light source may also be required, but is not always required, for example in the case of chemiluminescent measurement.

Any such light sensing means and/or the light source may be provided integrally with the measuring device. Preferably however, it or they are provided separately of the part of the device which is brought into contact with the sample fluid - e.g. a skin patch. This means that the device itself can be made disposable while the relatively more expensive light sensing means and associated electronics for example could be provided in a separate test meter.

In preferred embodiments the test device comprises means for optimising the light transfer from the sensing

means to the optically sensitive means. In a simple embodiment such means comprises a lens, e.g. integrally moulded as part of the support member for the test device. Additionally or alternatively the device may be arranged such that the light sensitive means views the sensing means along the conduit, e.g. microchannel, along which the sample fluid passes. In other words the conduit, preferably a microchannel, acts as a light pipe. This helps to enhance the optical density and therefore the signal achieved for a minimal sample volume, thereby making its measurement easier and more accurate. The material from which the conduit is formed is preferably chosen so to maximise light throughput at the frequencies of interest.

It will be appreciated by those skilled in the art that the arrangement described above is beneficial in its own right in enhancing the signal that may be measured from a minimal sample volume and thus when viewed from a yet further aspect the present invention provides an apparatus for measuring the light from an assay comprising an elongate conduit portion along which a sample fluid is drawn in use and a light sensitive means aranged to be sensitive to light coming substantially from the longitudinal axis of said conduit portion.

In one particularly preferred embodiment a disposable skin patch is provided with a moulded plastics lens over the analyte sensing means. A corresponding test meter is designed to be placed over the patch and comprises a light sensitive element which sits over the lens when the meter is placed over the patch. The meter may, in preferred embodiments, be arranged to be worn over the patch permanently and only removed in order to change the patch. This allows analyte measurements in blood or interstitial fluid to be taken with the user being completely isolated from contact with the fluid. The non-disposable portion

could even control a pump or the like for administering a substance such as insulin in response to the measured analyte concentration, e.g. via electrical, optical signals. An alternative arrangement might have the non-disposable portion acting directly on a reservoir on the patch to cause it to emit the substance.

So far various aspects of the present invention have been disclosed and discussed. One particularly important feature has been the use of microchannels in a clinical assay device, preferably, as discussed just above, with embedded electrodes therein. These have been disclosed, *inter alia*, for measuring blood glucose levels. However a further beneficial application of such arrangements is envisaged for blood coagulation testing.

Blood coagulation is an important phenomenon to monitor in many situations, particularly where a patient is taking drugs to control clotting e.g. after a heart valve replacement, deep vein thrombosis etc., since it is important to get the level of drugs correct in order to avoid the drug being ineffective on the one hand, or haemorrhage on the other hand. A useful measure of coagulation is the so-called prothrombin time. This is the time taken for a blood sample of given surface area to clot after reaction with a clotting agent such as a thromboplastin, e.g. Thromborel R or Thromborel S (trademarks) from DADE Behring.

Promthrombin time can be measured by allowing a blood sample to flow along a capillary until it stops flowing due to clot formation. Whilst this method works well for samples with good clot formation, those samples which do not clot well, i.e. have a long prothrombin time, are more difficult to measure using this arrangement since a poorly formed clot allows fluid to continue to 'creep' past i.e. the flow is not completely halted.

A further aspect of the present invention seeks to

improve upon this and provides a device for measuring clotting of a sample fluid comprising a microchannel as defined herein, and means for determining in use when or where flow of said fluid along said microchannel has stopped.

It will be appreciated that by incorporating a microchannel into such a measurement device, accurate determination of the time taken to clot can be achieved since even for samples exhibiting poor clot formation, the relatively small lateral dimensions of the microchannels defined herein mean that even a small amount of clotting should arrest the flow of fluid therein. Furthermore a microchannel will require less sample volume overall and can be coiled or otherwise fitted onto a reasonable surface area without having to compromise its length. Maximising the length of the channel is important in order to accommodate long clotting times - e.g. 20-30 seconds for blood, and to give greater measurement resolution.

The means for determining when flow has stopped may do so directly e.g. it may comprise a flow rate sensor, preferably one which senses such flow rate electronically. Clearly when the sensed flow rate is zero or at least below a threshold, flow is determined as having stopped.

Alternatively, the clotting time may be measured indirectly by measuring the distance along the channel which is travelled before flow is arrested.

Preferably the flow rate is measured by the rate of change in impedance between two electrodes across the channel. The electrodes can preferably be formed as described earlier. The resistive part of the impedance may be measured. For example an array of electrodes may be spaced along the channel to provide an incremental signal depending upon how far the blood sample has travelled. Alternatively a single large electrode might be provided along a wall of the channel, the resistance

between it and a counter electrode depending upon the degree with which the larger electrode is covered.

Preferably the purely capacitive component of the impedance is measured. This means that the electrodes need not be in contact with the sample fluid. Again a series of spaced electrodes could give a discrete reading or, preferably, a single pair of elongate electrodes could be formed - e.g. on opposing walls of the channel. It will be recognised that the capacitance between the two 'plates' will depend upon the extent to which the channel is filled with blood as a result the difference in relative permittivities (dielectric constants) of air and blood.

The capacitance of a parallel plate capacitor is given as follows

$$C = \frac{\varepsilon_o \varepsilon_r A}{d}$$

where:

ε_o = permittivity of free space
ε_r = relative permittivity of the dielectric between the plates
A = surface area of the plates
d = distance between the plates

Assuming that the electrodes have a constant width w and length l, this becomes

$$C = \frac{\varepsilon_o \varepsilon_r wl}{d}$$

Now if the channel is partially filled to a distance x with blood having a relative permittivity ε_1 and the rest of the channel is empty, having a relative

permittivity, e_2 the two adjacent sections of the channel may be considered as separate capacitors.

The capacitance of the filled portion is

$$C_{filled} = \frac{\varepsilon_o \varepsilon_1 \, wx}{d}$$

The capacitance of the empty portion is

$$C_{empty} = \frac{\varepsilon_0 \varepsilon_2 \, w(l-x)}{d}$$

Since these two capacitances are electrically in parallel, the combined capacitance is equal to their sum, i.e.:

$$C = \frac{\varepsilon_0 \varepsilon_1 wx}{d} + \frac{\varepsilon_0 \varepsilon_2 w(l-x)}{d}$$

$$= \frac{\varepsilon_0 w}{d} (\varepsilon_1 x + \varepsilon_2 l - \varepsilon_2 x)$$

By measuring the total capacitance, C and by knowing the other constants, the distance x, travelled by the blood may be calculated:

$$C = \frac{\varepsilon_0 w}{d} (\varepsilon_2 l + x(\varepsilon_1 - \varepsilon_2))$$

$$\frac{dC}{\varepsilon_0 w} = \varepsilon_2 l + x(\varepsilon_1 - \varepsilon_2)$$

$$x = \frac{1}{(\varepsilon_1 - \varepsilon_2)} \left(\frac{dC}{\varepsilon_0 w} - \varepsilon_2 l \right)$$

It will be seen from the above that as well as being able to monitor the rate of change of capacitance in order to determine the time taken for flow to stop, it is possible to measure the value, x, of the distance travelled by the blood before clotting. This gives a relative measure of the prothrombin time since the longer the blood takes to clot, the further along the channel it will progress. This can therefore be used, for example, as a cross check on the direct time measurement.

It will further be seen from the above equations that the capacitance, and in particular the change in capacitance achieved by introducing blood between the plates, is also inversely proportional to the distance between them, d. Thus it will be seen that a higher absolute change in the value of the capacitance, C may be achieved by having a channel whose cross-sectional dimensions are significantly smaller in the direction normal to the pates than in the direction parallel to them. Whilst giving a large capacitance change however, this might be inconsistent with the need for rapid arresting of flow on clot formation. Thus in an alternative embodiment a parallel array of microchannels is provided, each with a pair of electrodes, and the cumulative change in capacitance is measured. This can give an equally large change but without prejudicing the propensity of the flow to be arrested by a clot forming.

As well as the above application there are many other envisaged applications for a microchannel with electrodes therein and thus from a further broad aspect the present invention provides a device comprising a microchannel and a pair of electrodes therein.

Certain preferred embodiments of the invention will now be described, by way of example only, with reference to the accompanying drawings in which:

Figure 1a shows a first embodiment of the invention, in the form of a skin patch, in cross

section;

Figure 1b shows in cross section, the patch of Fig. 1a on a user's skin;

Figure 2 shows the layout of the skin patch of Figures 1a and 1b, in plan view;

Figure 3 depicts a cross section view of the skin patch of Figures 1a, 1b and 2 attached to the skin of the user with a controller unit attached to the skin patch;

Figure 4 depicts a display unit;

Figure 5 depicts schematically a further embodiment of the invention, showing the layout of a continuously-sensing skin patch;

Figure 6 depicts another embodiment of the invention, showing schematically a skin patch integrated with a needle, which also acts as an electrode, in cross section;

Figure 7 depicts schematically a skin patch with multiple microneedles acting as electrodes, in cross section;

Figure 8a shows a further embodiment of the invention, in the form of a single-use device with an integrated puncturing means;

Figure 8b is a cross section through a user's skin having the device of Figure 8a therein;

Figures 8c and 8d depict the construction of a device similar to that in Figure 8a

Figure 9 depicts a microchannel and optochemical sensor in plan view;

Figure 10 depicts a microchannel and electrochemical sensor in plan view;

Figures 11a to c are cross sections of the microchannel of Figure 10 with fluid progressively entering the channel;

Figure 12a is a close-up, partial, perspective view of a microchannel;

Figure 12b is a perspective view of a microchannel,

similar to that in Figure 12a;

Figure 13 depicts schematically a skin patch with an integrated insulin pump, in cross section;

Figures 14 and 15 depict schematically a device suitable for measuring blood clotting in cross-section and plan views, respectively; and

Figure 16 depicts schematically a device suitable for measuring blood clotting, similar to that in Figures 14 and 15 with a spiral microchannel.

Turning to Figures 1a, 1b and 2 there is shown a skin patch 2 suitable for measuring the level of blood glucose in a user. As may be seen in Figure 1a, the patch 2 is made up of several layers 3a-3c.

The lowermost layer 3a is made of polyester or polyimide, which is thin and flexible to allow it to be worn comfortably for a prolonged period of time, and has an adhesive on its underside to allow the patch to be securely attached to the skin of a user. Laminated to the lowermost layer is a substrate layer 3b. This supports an integrated hollow needle 4, an array of microchannel systems 8 and corresponding electrochemical detectors 12 and electro-osmotic pump systems 10. Each of these electrochemical detectors 12 and electro-osmotic pump systems 10 are electrically connected via conductive tracks (not shown) to respective terminals (not shown) at the edge of the patch. A controller unit 102 is pressed against these terminals in use in order to pass signals between the patch and a display unit 103 (see Figures 3 and 4).

The patch's low profile design not only makes it comfortable to wear but also relatively unobtrusive so that it can easily be concealed under clothing.

As mentioned above the substrate layer 3b of the patch 2 comprises an integrated hollow needle 4 whose length is chosen so as to penetrate into the skin by about 1.4 mm. The needle thus penetrates into the cutaneous layer of the skin, but not the subcutaneous

layer. This superficial penetration makes the device relatively painless, even when the needle resides within the skin for prolonged periods of time. This minimal penetration also means that the needle will not penetrate a blood vessel but will come into contact only with interstitial fluid. The needle 4 has a bore which is suitably sized (approximately 29 gauge) that it can draw up the interstitial fluid by capillary action.

The proximal end of the needle 4 is in fluid communication with a manifold 6 formed in the substrate layer 3b of the patch. Radiating out from the manifold 6 are eighteen of the microchannel systems 8.

One such microchannel system 8 is shown in greater detail in Figure 10. The microchannel itself 126 is etched into the substrate layer 3b and is approximately 50μm wide, 50μm deep and 10 mm long. The microchannel 126 is in direct communication with the manifold 6 into which the fluid flows from the needle 4. Downstream of the manifold 6 is an electrode system comprising a pair of gold electrodes 127a, 127b. The electrodes are formed on a second substrate layer 3c (omitted from this figure for clarity) by printing or sputtering. The second substrate layer is then laminated onto the first substrate layer 3b thereby closing the microchannel 126 and bringing the electrodes 127a, 127b into contact with it. The electrodes 127a and 127b are positioned adjacent to each other, together forming an electro-osmotic pump system. By applying a voltage difference across the electrodes 127a and 127b, an electric field is generated along the microchannel. This electric field drives fluid along the microchannel 126.

About halfway along the microchannel 126 is a hydrophobic gate 128. The hydrophobic gate 128 is a patch of polystyrene which is also coated on the upper substrate layer of the patch. By virtue of its hydrophobic nature (in contrast to the hydrophilic properties of the microchannel 126). This patch 128

prevents the flow of fluid by capillary action along the microchannel 126. Downstream of the hydrophobic gate 128 is an electrochemical sensor 12 comprising two carbon electrodes 132a and 132b also formed on the upper substrate layer 3c. After being formed on the substrate layer 3c, the two electrodes 132a, 132b are covered with a layer 131 of glucose oxidase and ferricyanide, thereby forming the electrochemical detector 12.

A further hydrophobic gate 130, similar to the first, is provided downstream of the sensor 12. It will be understood by those skilled in the art that the hydrophobic gates may be constructed of any suitable material, including, but not limited to, PTFE, polycarbonate, polyisobutelene, PMMA, dodecyl acetate, silicon rubber, synthetic way, octadocyl mercaptane, dodecyl mercaptane, and/or octa decyltrichloro silane.

A control unit 102 for the patch 2 is shown in Figure 3. As may be seen, this sits on top of the patch 2 and is secured by further strips of adhesive on the upper side of the patch (not shown). The control unit 102 has an array of resiliently biassed leaf contacts on its underside which contact the upper sides of the four electrodes 127a, 127b, 132a, 132b of each respective microchannel 126.

The control unit 102 is battery operated and is capable of transmitting signals to a wireless display unit (Figure 4) using the Bluetooth communications protocol.

Operation of the skin patch 2 will now be described. The patch is attached to the skin of a user causing the needle 4 to penetrate into the cutaneous layer of skin. Cutaneous fluid is drawn up the needle 4 and into the manifold 6 of the patch by capillary action. Referring now to Figure 11a it will be seen that the fluid 136 is drawn into the microchannel 126 by capillary action as far as the hydrophobic gate 128 where its flow is arrested. When a measurement is

required, the controller unit 102 issues an appropriate signal to the electro-osmotic pump 10, in the form of a voltage difference across the two electrodes 127a, 127b. This drives the fluid 136 to flow over the hydrophobic gate 128 and sensor 12 as far as the next hydrophobic gate 130 as may be seen in Fig 11b.

Once the interstitial fluid 136 comes into contact with the sensor 12, glucose oxidase catalyses the oxidation of glucose to glucono-1,5-lactone, releasing electrons. These are transported to the electrodes 132a, 132b by the ferricyanide electron shuttler, thereby giving rise to a electric current resulting from electron transfer to the electrodes 132a, 132b from the glucose oxidase which is measured by the control unit 102. The measurement is chrono-amperimetric - i.e. current is used to determine the glucose concentration. In an alternative embodiment however an end point test could be performed in which the cumulative charge transfer is measured.

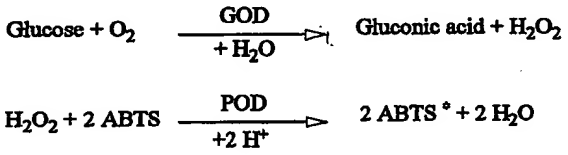
Since the volume of the microchannel 126 is small, only a small amount of interstitial fluid 136 is required to carry out the measurement. Moreover the volume of test fluid is precisely controlled since the fluid is prevented from continuing to flow along the microchannel 126 by the second hydrophobic gate 130. In some circumstances however it may be that the initial test was unsuccessful . If this is determined to be the case, the controller may apply a higher voltage across the electrodes 127a, 127b of the electro-osmotic pump 10. The resultant additional driving pressure causes the fluid additionally to breach the second hydrophobic gate 130. This will bring fresh fluid into contact with the sensor 12 and thereby allow the test to be repeated.

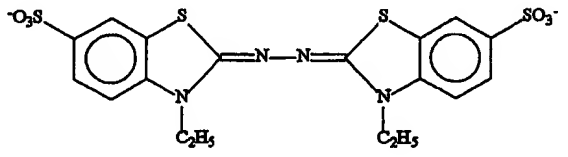
The controller unit 102 is pre-programmed to initiate the flow of interstitial fluid sequentially to each of the eighteen detectors 12 to enable frequent testing during a short period (e.g. 8-24 hours). Thus

if a 24 hour monitoring period is required, the controller will be set to issue each consecutive signal every 1.3 hours. However, the user can force the controller to issue the next signal early if he or she requires an immediate test by selecting this from the controller. Once all the tests on the patch 2 have been performed, the controller 102 transmits a signal to the display means 103 to alert the user so that the patch 2 can be discarded and a fresh one applied.

To change the patch 2, first the controller unit 102 is detached from it and the patch is then peeled off the user's skin. A new patch may be applied and the controller is then attached to by means of the fresh adhesive strips on the new patch.

An alternative form of microchannel 126 is shown in Fig. 9. This is similar to that shown in Fig. 10 except that the electrochemical sensor 12 is replaced by an optochemical one 12. The optical sensor 12 comprises a reaction chamber 129 which contains Glucose oxidase (GOD) and Horseradish Peroxidase (POD) and a leuco-dye, namely 2,2-Azino-di-[3-ethylbenzthiazoline-sulfonate] (a colourless precursor of the dye molecule). The reaction which takes place is as below:





Substrate / oxidized form of ABTS

It will be seen from the above that the dye changes colour in accordance with the amount of glucose in the sample. In order to measure this, the chamber 129 has a transparent upper surface. This is arranged to be aligned with the tip of an optical fibre in a modified control unit (not shown) so that the fibre is approsimately 2 to 3 mmm above the dye spot. The other end of the fibre is in optical contact with a light source and light sensitive diode sensor. The diode is sensitive to light at 438nm which is the absorption wavelength of the transformed dye. The degree of absorption therefore gives a measure of the amount of transfomred dye and thus the amount of glucose present.

As in the previous embodiment, the controller (not shown) issues an electrical signal to the electro-osmotic pump system 10 in the form of a voltage difference across the electrodes 127a and 127b to drive the interstitial fluid along the microchannel 126, past the hydrophobic gate 128 and into the reaction chamber 129. The glucose present in the fluid acts as a substrate for GOD, which breaks the glucose down into glucono-1,5-lactone hydrogen peroxide. POD subsequently catalyses the oxidation of the leuco-dye using the hydrogen peroxide, resulting in the production of a coloured dye. The light source (not shown) emits a beam of light and how much of this light is transmitted through chamber 129 is detected.

The controller converts the dye concentration to a glucose concentration and transmits this to the display unit 103 in a similar manner to the previous embodiment.

Those skilled in the art will understand that instead of
2,2-Azino-di-[3-ethylbenzthiazoline-sulfonate], any suitable leuco-dye may be used, e.g.
Tetramethylbenzidine-Hydrochloride, or
3-Methyl-2-Benzothiazoline-Hydrazone in conjunction with 3-Dimethylamino-Benzoicacide.

The microchannels described as hereinbefore use electrochemical or colorimetric means to detect glucose. The skilled person would understand that other detection means, such as infra red detection, filter photometry or Kromoscopy may be used.

Figure 5 shows another preferred embodiment of the invention, also in the form of a skin patch 20. The patch 20 has a similar construction to that of the first embodiment and thus it has a hollow needle 4 which in use penetrates the cutaneous layer of skin of the user. When the patch is applied, the needle 4 directs cutaneous fluid into the manifold 6, which is in turn in fluid communication with a microchannel 22. An electrochemical detector comprising a layer of glucose oxidase is provided at the proximal end of this microchannel 22.

In contrast with the previous embodiment however, the glucose detector 24 is of the continuous type. In this embodiment therefore the cutaneous fluid is continuously drawn across the detector 24 and into the sink 27. The glucose detector 24 therefore continuously measures the glucose concentration. A further microchannel 26 leads the fluid from the continuos detector 26 to a sink for waste fluid 27.

The continuous sensor is formed by electrodes manufactured by the metal deposition technique. The continuous sensor is coated with glucose oxidate, and detects the hydrogen peroxide released when the glucose oxidase catalyses the oxidation of glucose. In this configuration, no electron mediator is required

Also in fluid communication with the microchannel 26, downstream of the continuous glucose sensor 24, are six additional microchannels 28, each of which leads to a respective single-use glucose sensor 30. These microchannels are arranged in the same way as that shown in Fig. 9 and thus include hydrophobic gates and an electro-osmotic pump, although these have been removed

from the diagram for clarity. The sensors 30 are of the same type as those 12 in the first embodiment. Each glucose sensor 30 has an electrically conductive track 32 leading from it to the edge of the patch 20. The electro-osmotic pumps are controlled by the controller unit (not shown) so that the fluid is only pumped along a given microchannel 28 when an appropriate signal is received from the controller.

In the use of the patch 20, interstitial fluid is made to flow continuously through the needle 4 and the first microchannel 22, and thus over the electrochemical glucose sensor 24, to the sink 27 by means of capillary action. Periodically, the electro-osmotic pump in one of the additional microchannels 28a in communication with the main microchannel 26 is activated, and the fluid is pumped through the microchannel 28a to the single-use detector 30a.

The single-use sensors 30 are used to re-calibrate the continuous sensor 24, thereby correcting for any drift of thereof during use. This obviates the need for a user to perform a manual fingerstick test as is necessary with previously known arrangements. Furthermore the low sample volume resulting from the use of microchannels means that the continuous sensor can rapidly equilibrate when it is first used. When all the calibration tests have been used or the slope of the calibration curve has drifted below a critical value, e.g. as a result of the electrode becoming fouled, the patch may be discarded and a fresh one applied. The critical value of the calibration curve slope will depend upon the gain of the the amplifying circuit employed and may be readily determined by those skilled in the art.

Thus it will be seen that in some of its preferred embodiments, the present invention allows a continuous measurement of glucose within cutaneous fluid from which the blood glucose level can be inferred. Detector drift

is corrected by the use of calibration sensors found within the patch, which test the same fluid, and can thus be compared directly to the output of the continuous sensor in order to re-calibrate it.

Figure 6 shows schematically a further preferred embodiment of the invention, also in the form of a skin patch 114. The patch 114 has a similar construction to that of the previous embodiments and thus it has a hollow needle 106, 1.4mm long and 0.3mm wide which penetrates the cutaneous layer of the skin 113 of the user, also known as the epidermis. Again, the needle does not penetrate the dermis. It is therefore relatively painless.

In this embodiment however the needle 106 also acts as an electrode within the epidermis 113. Two further electrodes are provided 108 and 109 on the substrate layer. All three electrodes 106, 108 and 109 are electrically connected via conductive track (not shown) at the edge of the patch. By applying a voltage difference across the electrodes 106, 108 and 109, an electric field is generated along the needle 106 and manifold 111. This electric field stimulates the skin and drives fluid out of the skin along the needle 106, through the manifold 111, along the microchannel 110 to the sensor (not shown). This therefore enhances the inherent capillary action.

Figure 7 is similar arrangement to that of Figure 6, but in which multiple microneedles 106 are provided, in place of the single needle 106. These microneedles are 400 micrometres in length and thus penetrate the cutaneous layer of skin in a substantially pain free manner.

The needles 106 are formed by integrally moulding suitable formations on the the plastics substrate layer and then electroplating the formations to give the an outer metallic layer. In this embodiment nickel is used, although platinum, gold or any suitable alloy of

two or more of these may be used. Alternatively the needle or array of needles could be laminated onto teh substrate layer.

Figures 8a to 8d show two further embodiments of the invention. In contrast with the foregoing embodiments, these are both single-use strips suitable for measuring blood glucose of a user. They are therefore used in a similar way to conventional test strips. However a principle difference is that each has an integrated lance 119 at one end.

Considering the device 115 shown in Fig 8a, it will be seen that it is made essentially of two layers 116 and 117. The lowermost substrate layer 116 is made of polyester and comprises a microchannel 118 integrally moulded into it as well as the integrally moulded lance 119 arranged in close proximity with the entrance 103 of The microchannel. During manufacture, the microchannel 118 is coated with glucose oxidase, which can be applied by any conventional means, such as ink-jet or spray coating during manufacture.

The uppermost layer 117 has laminated onto its underside an electrode system 121, which forms the electrochemical detector. This electrode system 121 comprises three electrodes 221 of which at least one is covered with layers of glucose oxidase and ferricyanide to form a working electrode for detecting glucose, as is well known in the art. Corresponding tracks 321 allow electrical connection to be made to the electrodes at the distal end of the strip when it has been inserted into a suitable test meter. The upper layer 117 is slightly longer than the lower one 116 to allow access to the tracks 321 for this purpose.

It will be noticed in particular that the lance 119 of the strip 115 in Fig 8a is essentially V shaped in cross section and tapers towards its tip. This means that when it is used to puncture a user's skin 123, as is shown in Figure 8b, the two sides of the V force back

a portion of the skin 123, forcing the epidermis to form the remaining wall 123 of an enclosed channel 124. Thus an open channel is effectively transformed into a closed one when it is inserted into skin. This allows fluid to be drawn up the channel 124 so formed and into the microchannel 118, without having to mould a very fine hollow needle or provide a fragile extrusion on the upper lamination 117.

The microchannel 118 is also formed with a V shaped profile for convenience of fabrication, but this is not essential as may be seen from the slightly modified embodiment of Figs 8c and 8d in which the microchannel 118' has a rectangular profile.

In the use of the strip 115, the user pierces their skin with the lance 119 and interstitial fluid or blood (depending on the length of the lance 119) is made to flow, by means of capillary action, through channel 124 formed by the lance and the skin 122, into the microchannel 118 and thus over the electrochemical detector 121.

The user then withdraws the strip 115 and inserts the opposite end into a conventional style test meter which makes electrical connection to the three conductive tracks 321. At the detector 121, the concentration of glucose in the fluid drawn up is measured by measuring the electric current resulting from electron transfer to the electrode from the glucose oxidase.

Figure 13 shows schematically the arrangement of a further embodiment of the invention in which an insulin pump system is integrated with a glucose testing skin patch 210. The patch 210 is similar to those described earlier and thus will not be described again in detail save to mention that it has a flexible substrate layer 216, which has an adhesive underside to allow the patch to be attached to the users skin.

In contrast with the patches described previously

however, two needles are attached to the substrate layer of the patch. The first is an integrated microneedle 217 in direct communication with a manifold (not shown) from which radiates an array of microchannels 215 and this needle is therefore as previously described. The second needle 212 is substantially longer as it is required to inject insulin into the user's bloodstream. This needle 212 is also integral with the support member 216, and is connected to a reservoir 211 containing insulin which is formed on the support member 216. A micropump 213 is provided between the reservoir 211 and the needle 212 which can pump insulin from the reservoir to the needle and into the user's bloodstream upon receipt of an appropriate signal.

In use the radiating array of microchannels and glucose sensors are used in the same manner as described for the embodiment of Fig 2 to measure the level of glucose periodically. In this case however, the controller uses the determined glucose level to calculate a quantity of insulin to administer to the user in order to bring their glucose level within a specified range.

The above preferred embodiments of the invention have related to the testing of interstitial fluid. It will be understood by the skilled reader that any suitable bodily fluid, can be used instead, e.g. blood, urine, spinal fluid, lymph, saliva, sweat or seminal fluid. The patches described previously relate to the measurement of glucose in a body fluid. However, any suitable analyte may be measured, including and not limited to cholesterol, lactate, hormones, antibodies, illegal drugs or alcohol, or indeed any other appropriate analyte known to those skilled in the art.

Figure 13 shows schematically the arrangement of a further embodiment of the invention in which an insulin pump system is integrated with a glucose testing skin patch 210. The patch 210 is similar to those described

earlier and thus will not be described again in detail save to mention that it has a flexible substrate layer 216, which has an adhesive underside to allow the patch to be attached to the user's skin.

In contrast with the patches described previously however, two needles are attached to the substrate layer of the patch. The first is an integrated microneedle 217 in direct communication with a manifold (not shown) from which radiates an array of microchannels 215 and this needle is therefore as previously described. The second needle 212 is substantially longer as it is required to inject insulin into the user's bloodstream. This needle 212 is also integral with the support member 216, and is connected to a reservoir 211 containing insulin which is formed on the support member 216. A micropump 213 is provided between the reservoir 211 and the needle 212 can pump insulin from the reservoir to the needle and into the user's bloodstream upon receipt of an appropriate signal.

In use the radiating array of microchannels and glucose sensors are used in the same manner as described for the embodiment of Fig 2 to measure the level of glucose periodically. In this case however the controller uses the determined glucose level to calculate a quantity of insulin to administer to the user in order to bring their glucose level within a specified range. The controller then issues a signal to the micropump 213 to activate it and thus pump insulin from the reservoir 211 for an appropriate length of time corresponding to the desired dose. In this way, the device essentially provides a closed-loop, self-contained system which can maintain glucose levels within acceptable ranges and which only requires user intervention to replace consumable elements such as the patch.

A further application of the principles of the invention will now be described with reference to

Figures 14, 15 and 16. In this application, the time taken for the flow of a sample of blood to be arrested by clot formation clot is measured. Also measured is the distance along the microchannel which the blood flows. Figure 14 is a cross-sectional view of an embodiment of such a device. This device comprises an elongate support member 200. A microchannel 202 is etched into the upper surface of the support member with dimensions of approximately 10 micrometres by 50 micrometres. A second substrate layer 203 is laminated on top of the support member 200, thereby closing the open microchannel 202. A carbon electrode 201a is formed on the upper surface of this second substrate layer 203 and it will be seen that there is a corresponding electrode 210b formed on the underside of the support member 200 in alignment with the microchannel 202. As will be seen from the plan view of Figure 15, the upper electrode 201a is substantially coextensive with the microchannel 202 but extends beyond one end thereof to the edge of the support member 200 to form an edge connection 204. Although not visible in Figure 15, the lower electrode 201b is similarly arranged.

Prior to laminating the upper substrate layer 203 onto the support member 200, the walls of the microchannel 202 are coated with a thin layer of Thromborel R (trademark), a thromboplastin clotting agent available from DADE Behring.

In use, a sample of blood is applied to the end of the microchannel 202 and a timer is started. The blood is drawn into and along the microchannel 202 under capillary action. As the blood flows along the microchannel 202, its contact with the clotting agent causes it to clot. This eventually arrests the flow of blood part-way along the channel.

The two electrodes 201a, 201b are connected into a measurement circuit (not shown) via connections 204 at

the edge of the strip. This circuit is used to measure the capacitance between the two electrodes. This may be done in any way known in the art e.g. by including the device as part of an RC oscillator and measuring its frequency (which is inveresely proportional to the capacitance). As the blood flows, the capacitance between the two electrodes 201a, 201b will change. However, when the rate of change falls to zero, it may be deduced that the flow has been arrested and the timer is therefore stopped.

The actual prothrombin time measured is divided by a normalising factor, the time in which normal blood would clot taking into account the dimensions of the channel and the properties of the clotting agent. The result, in the form of an International Normalised Ration (INR) is displayed on a readout (not shown).

It will further be appreciated by those skilled in the art that the capacitance between the two electrodes 201a, 201b is proportional, *inter alia*, to the relative permittivity of the contents of the microchannel. The relative permittivity of blood is assumed to be approximately the same as that of water and alising is thus of the order of 80. On the other hand, the relative permittivity of air is approximately 1).

Accordingly, the overall capacitance between the two electrodes 201a, 201b will depend upon the proportion of the microchannel 202 which is filled with blood. An alternative estimate of the prothrombin time of the blood may therefore be obtained by measuring the value of the capacitance. This is calibrated empirically against the prothrombin times and is used to indicate an error requiring a repeat measurement if the two are not consistent.

An alternative embodiment is shown schematically in Figure 16. It will be seen that in this embodiment, the microchannel 202 is spiral shaped in order that an increased length can be achieved for a given surface

area of the device. This is beneficial since it can allow the same capacitance change using a thinner microchannel, the latter being beneficial since clot formation will more easily arrest blood flow in a thinner channel. A further alternative would be to provide a plurality of straight channels in parallel.

Figures 12a and 12b show a possible alternative configuration in which the microchannel 300 is flanked by a series of longitudinally spaced pairs of electrodes 38 integrally formed in the walls of the microchannel 300. In order to form these electrodes 38, firstly a series of parallel channels 34 is cut into the substrate material 302. The channels 34 are then filled with carbon to make them electrically conductive. The microchannel 300 is thereafter formed at right angles to the parallel channels 34 such that it intersects them. This creates the opposing electrodes 38 on each side of the microchannel 300.

This arrangement allows the progress of blood along the microchannel 300 to be monitored by measuring the electrical resistance between adjacent pairs of electrodes 38. As the blood reaches each successive pair, the resistance will fall from open-circuit, to a value of the order 200 kilohms. Thus a discrete reading for the distance travelled is obtained. This arrangement also demonstrates that the electrodes 38 may be allowed to come into contact with the blood.

It will be appreciated by those skilled in the art that whilst some of the potential embodiments of the inventive concepts disclosed herein have been described in greater detail, there are many different variations and modifications to these possible. For example, devices in accordance with the invention may measure the concentration of analytes other than those in bodily fluids.

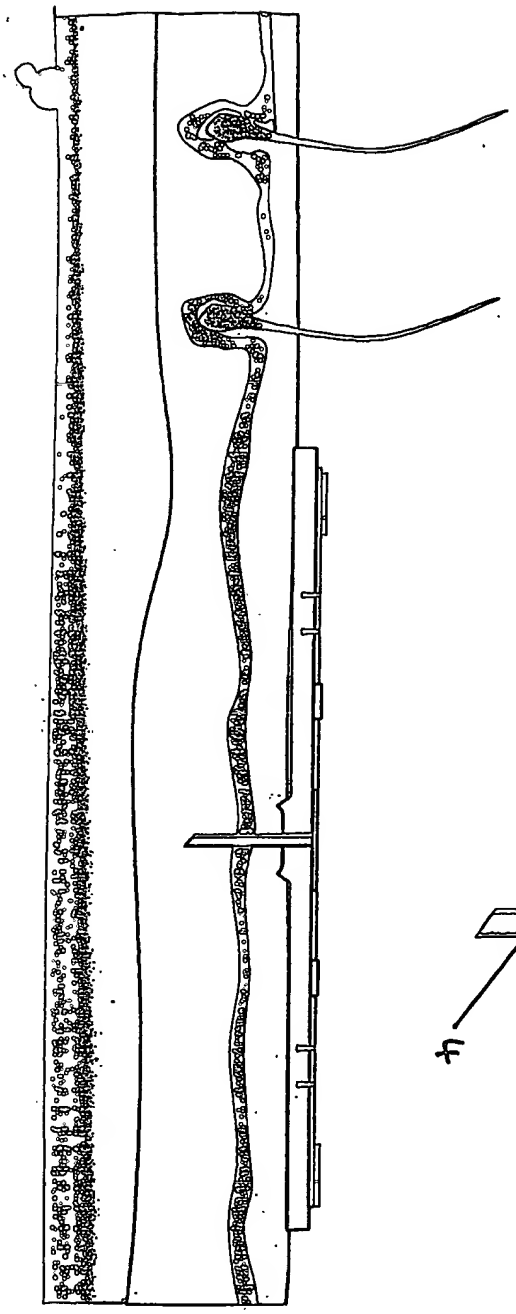


Fig 1b

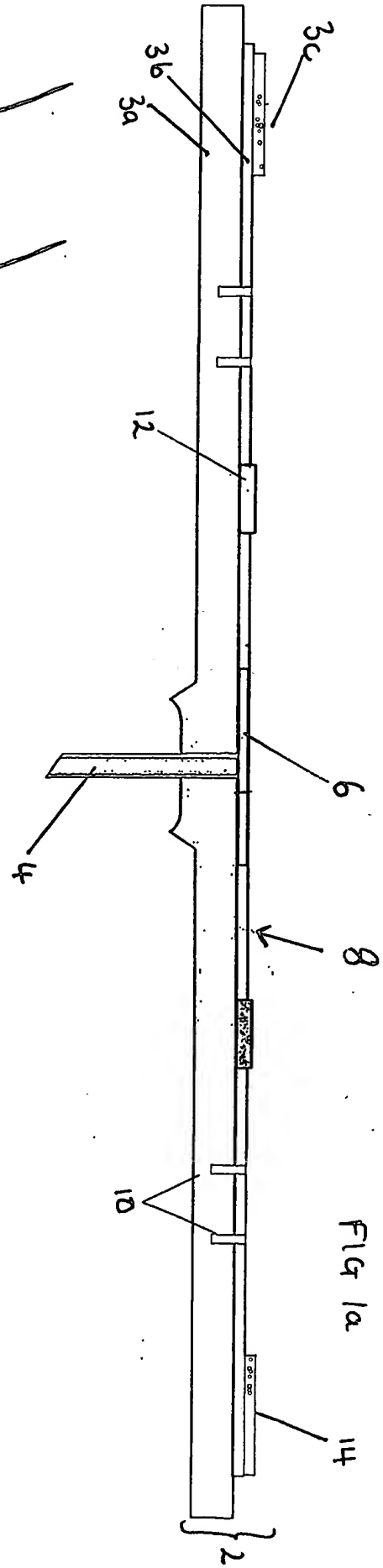


Fig 1a

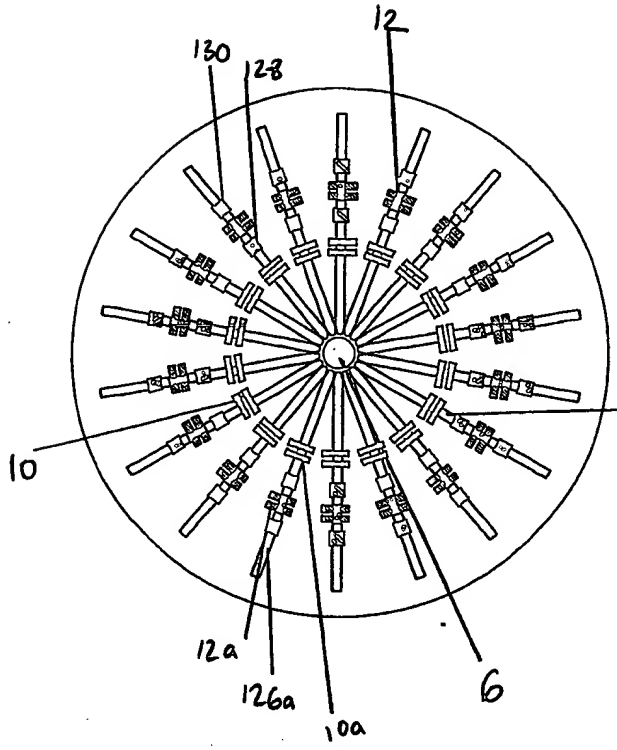


FIG2

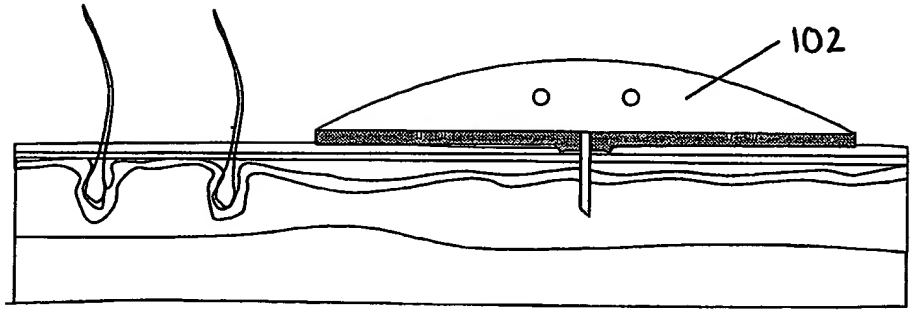


FIG3

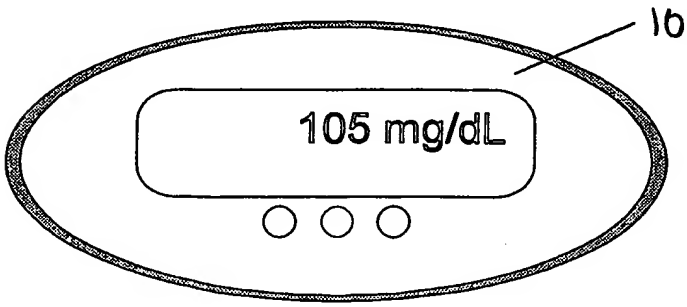


FIG4

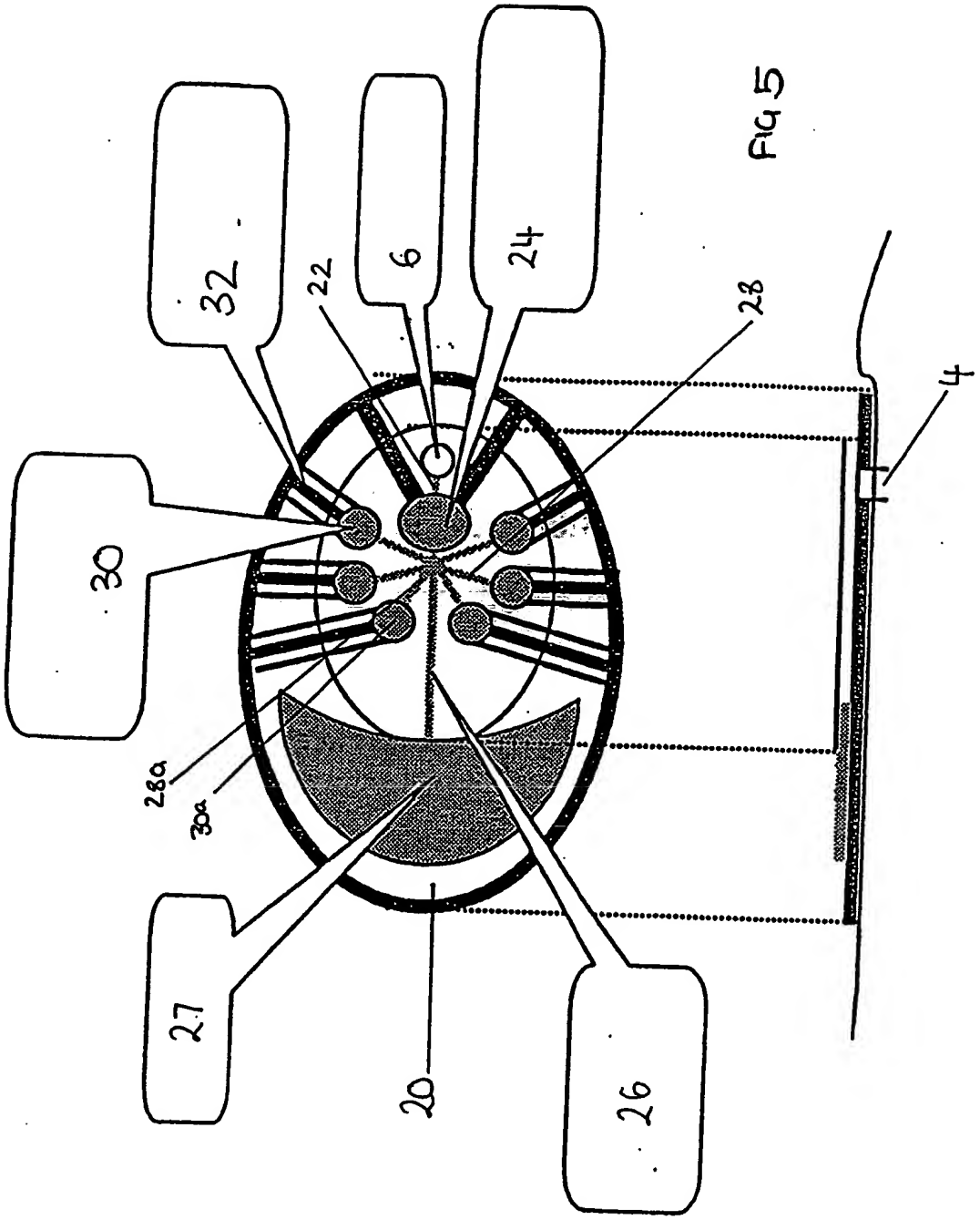


Fig 5

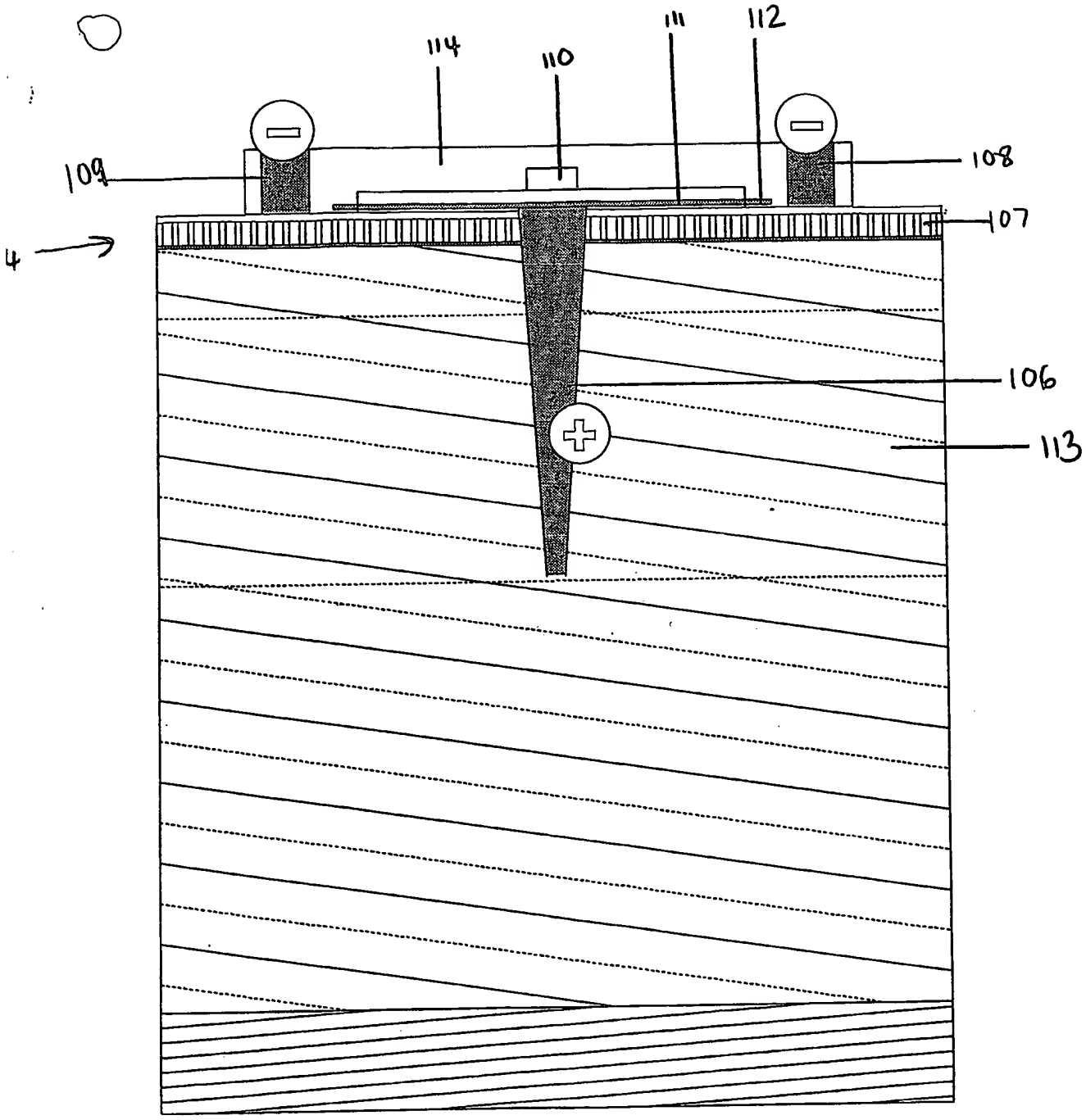


FIG 6

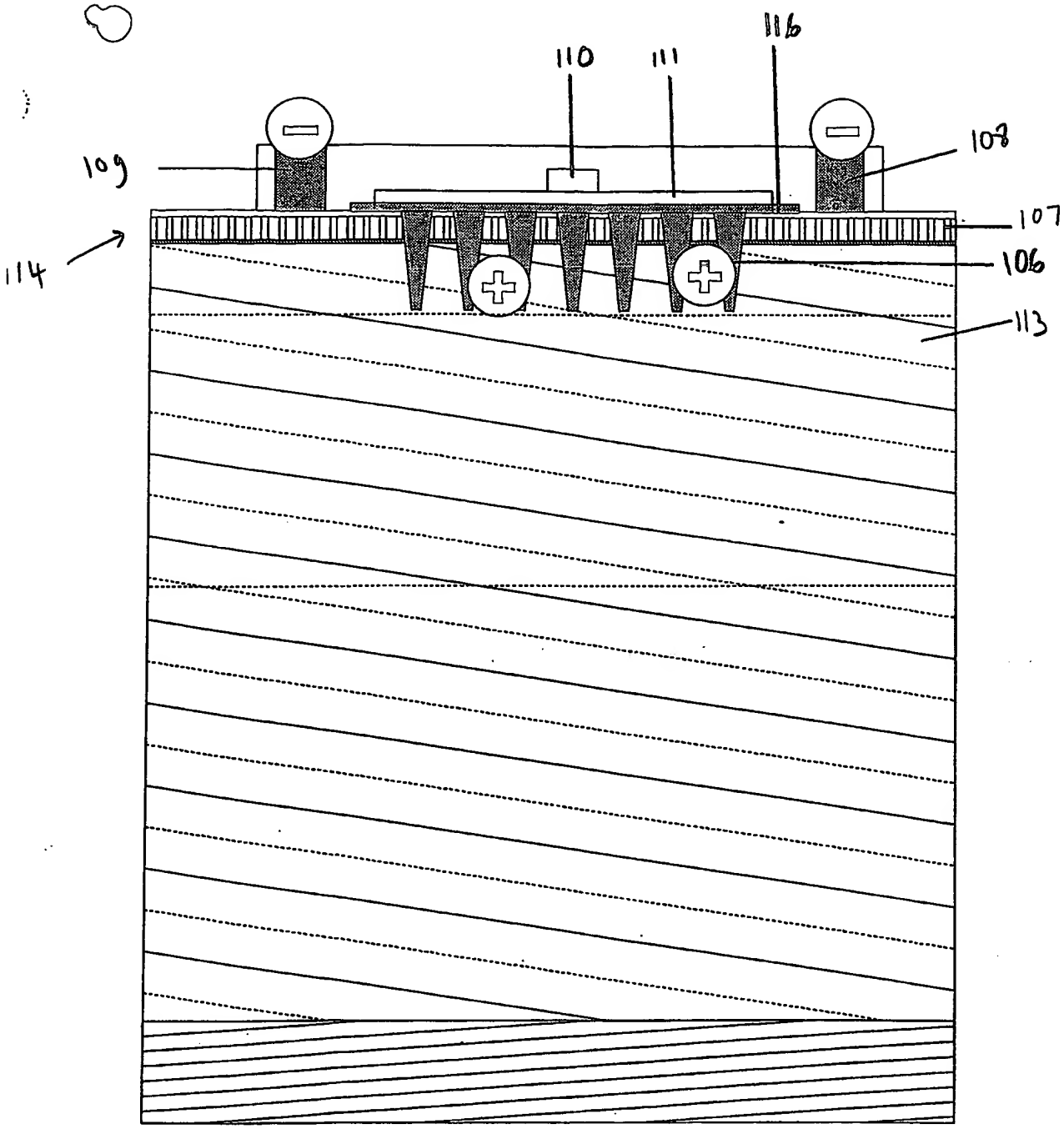


FIG 7

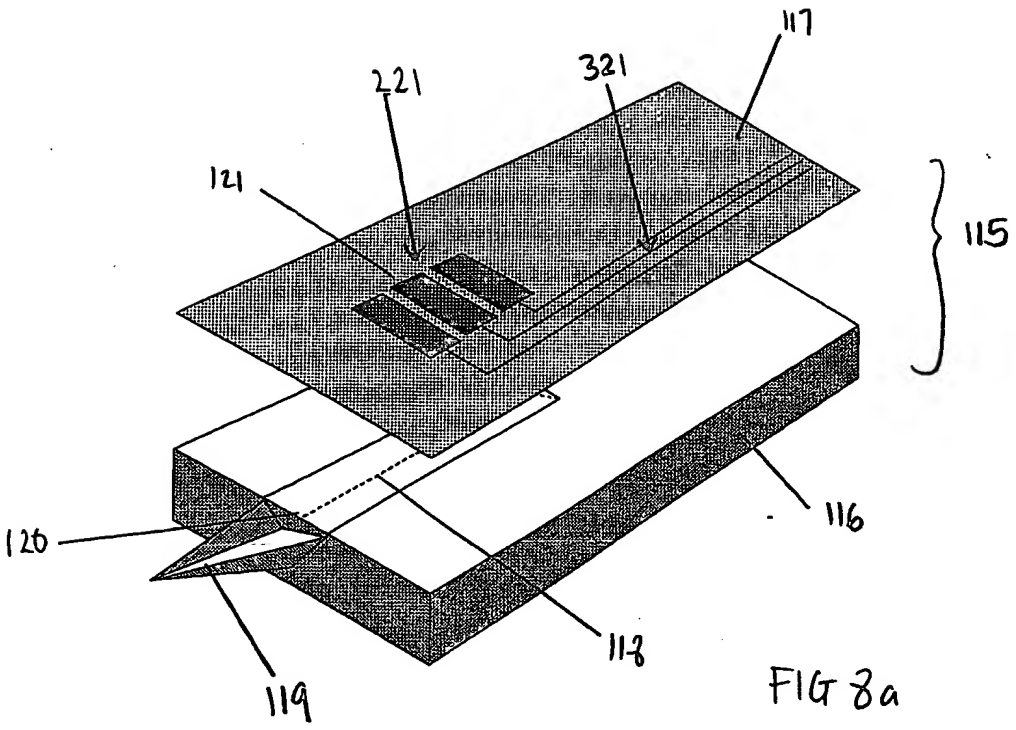


FIG 8a

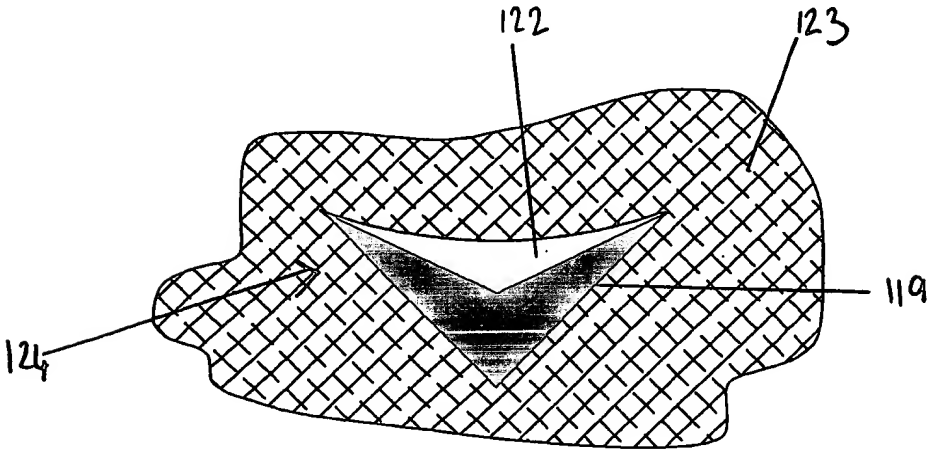
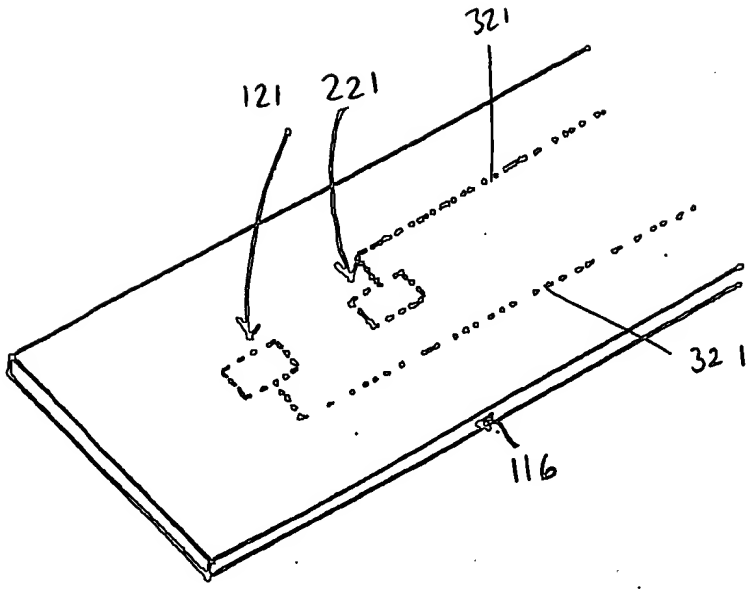


FIG 8b

FIG 8c



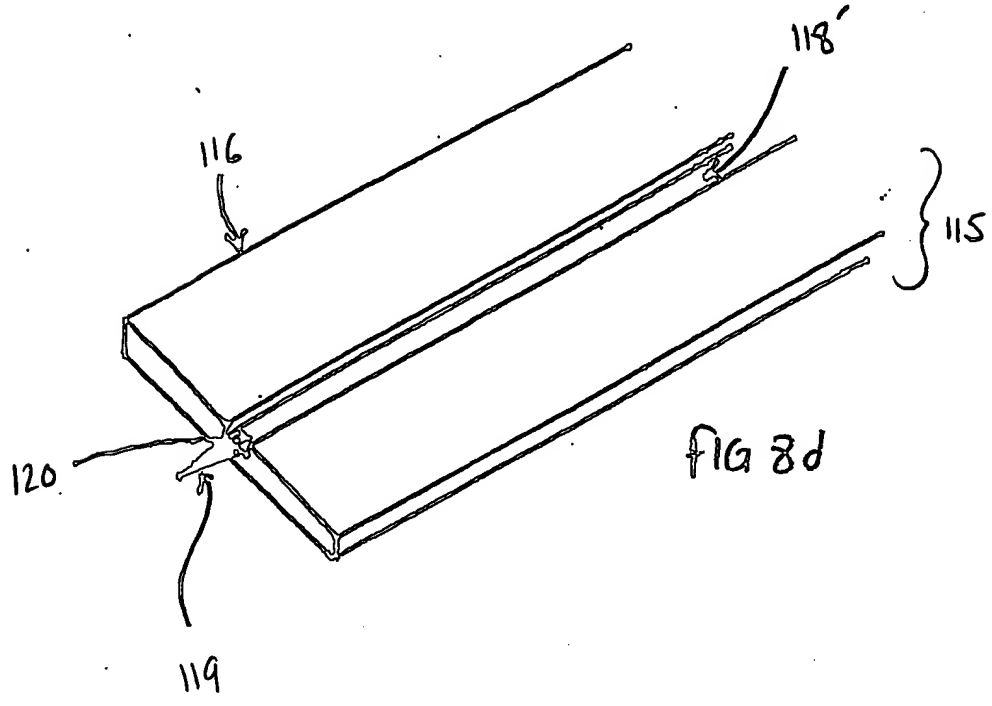


FIG 8d

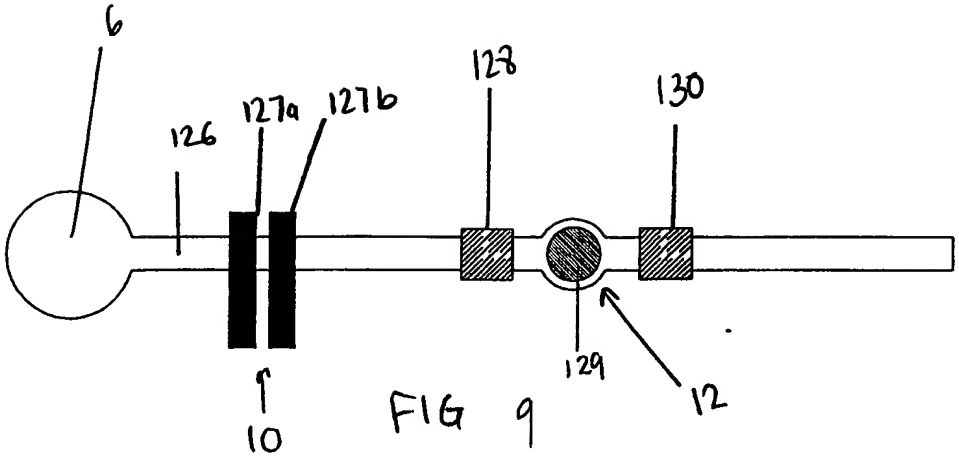

6
126
127a
127b
128
130
129
12
10

FIG 9

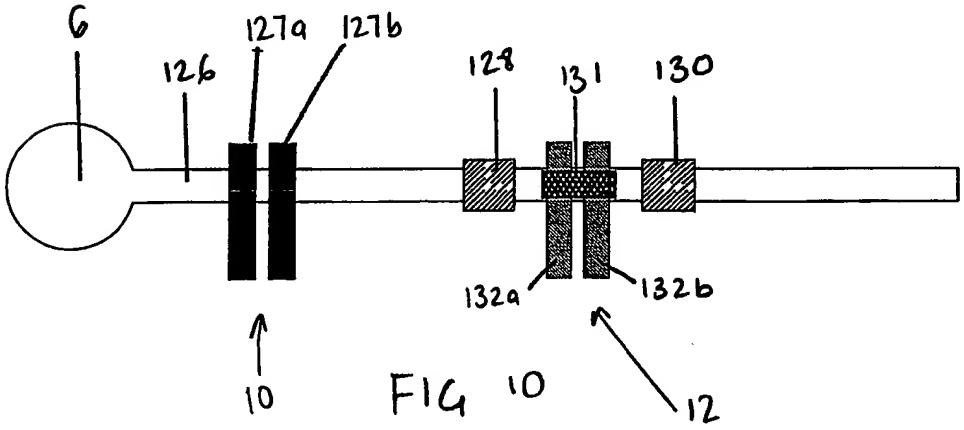

6
126
127a
127b
128
131
130
132a
132b
10
12

FIG 10

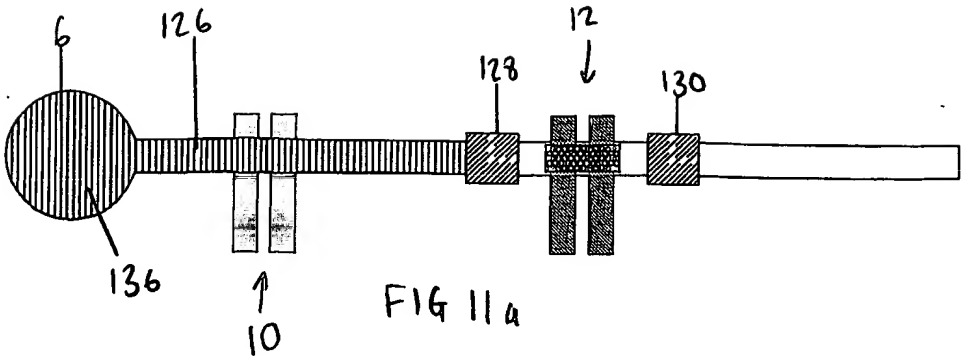


FIG 11a

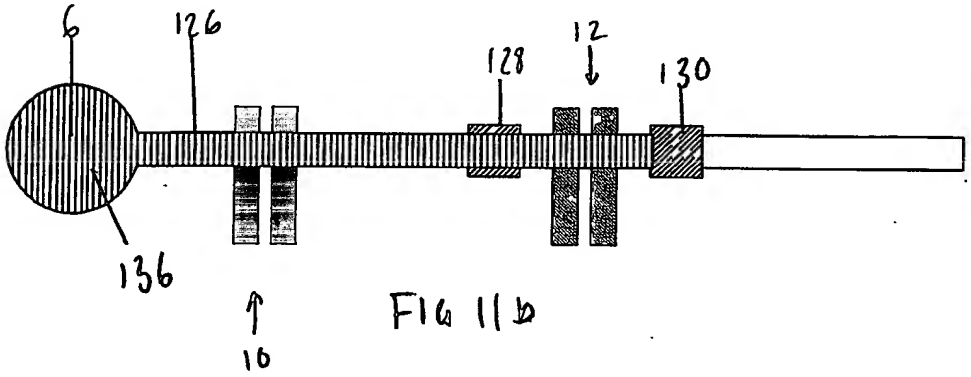


FIG 11b

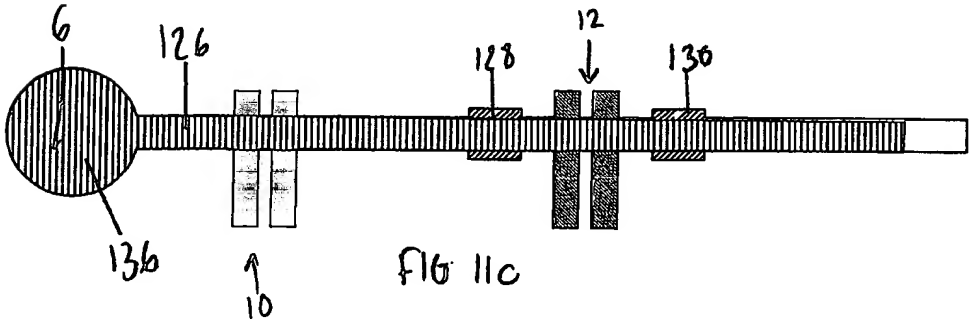


FIG 11c

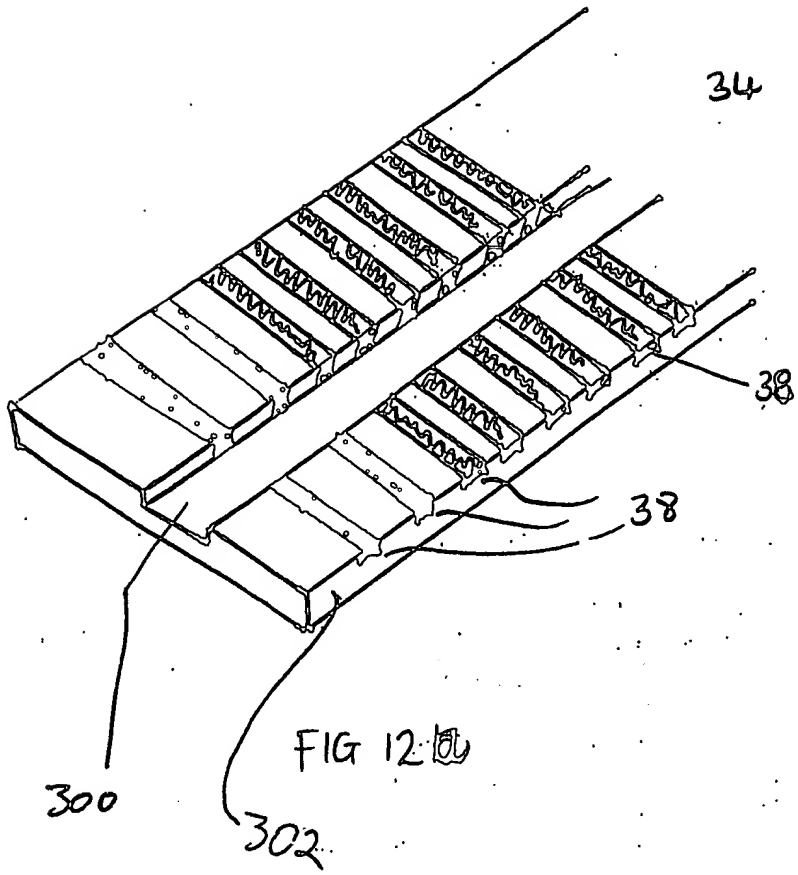


FIG 12b

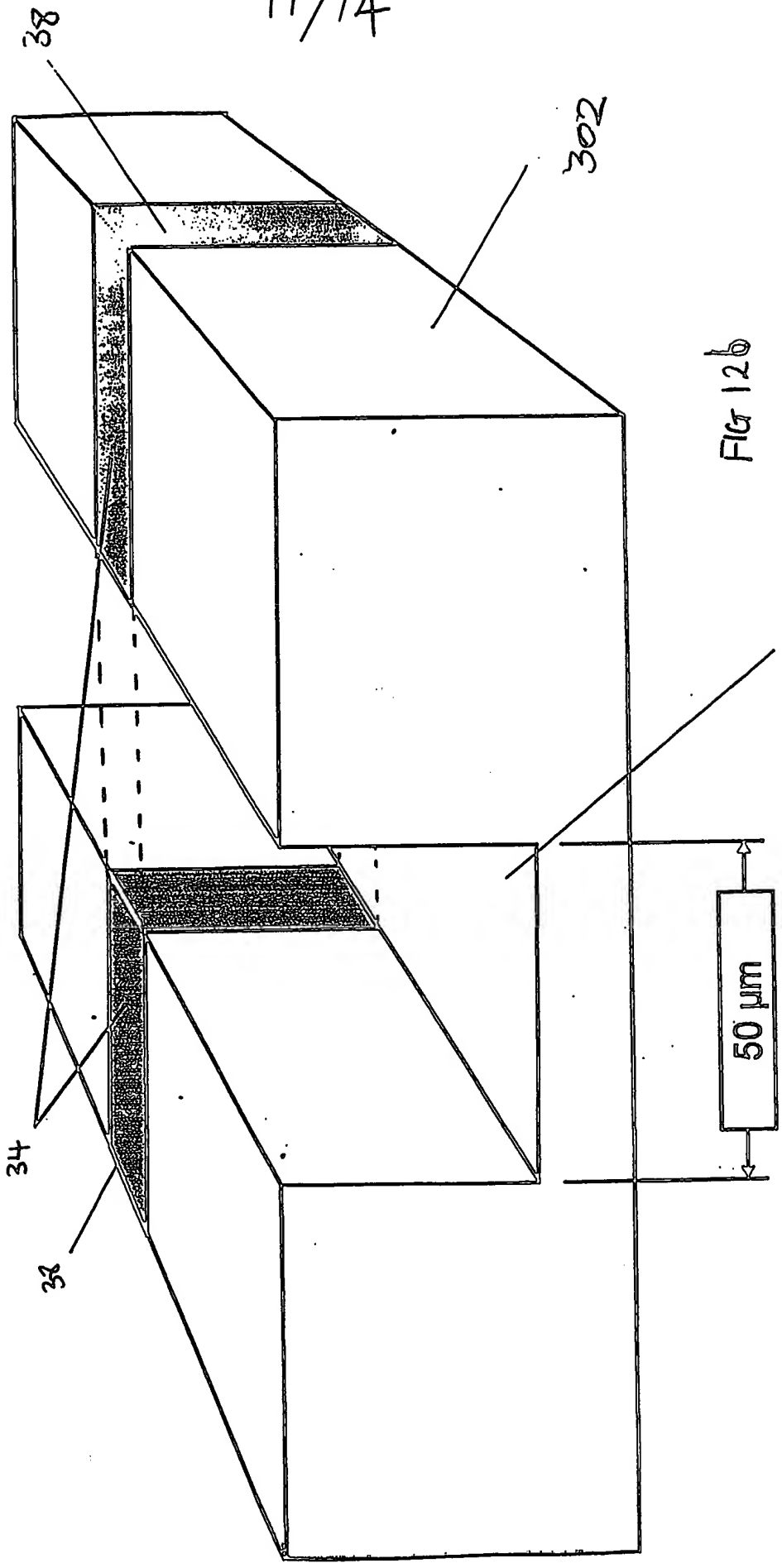


Fig 12b

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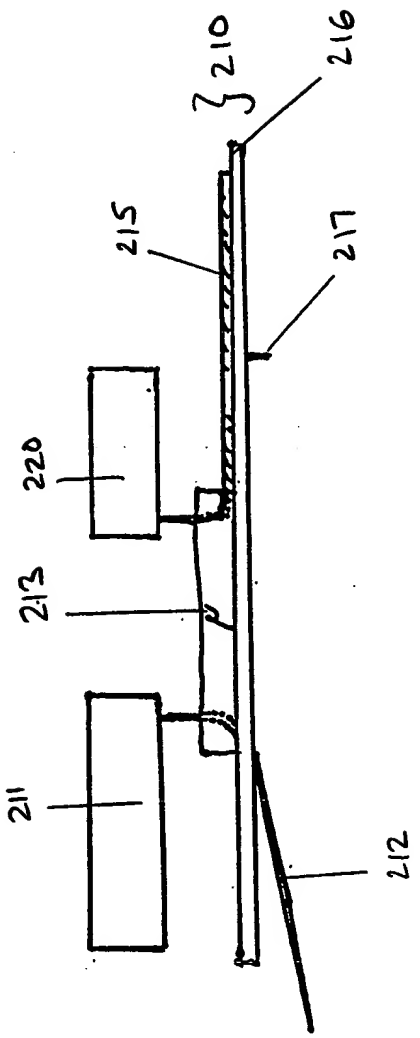

FIG 13

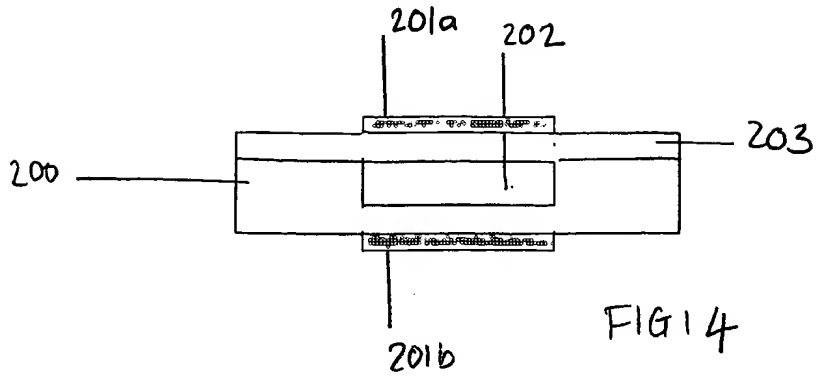

FIG 14

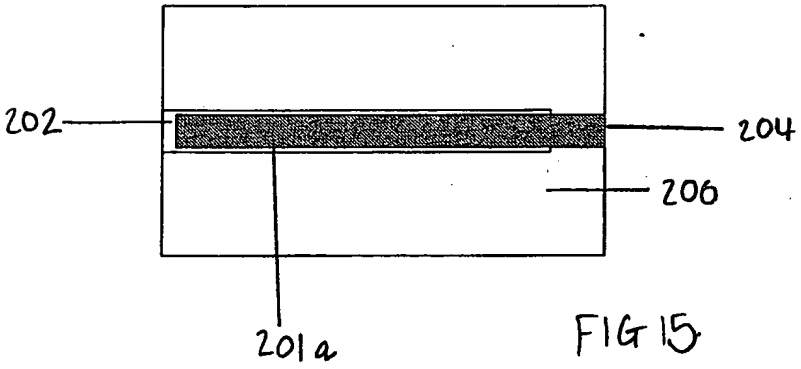

FIG 15

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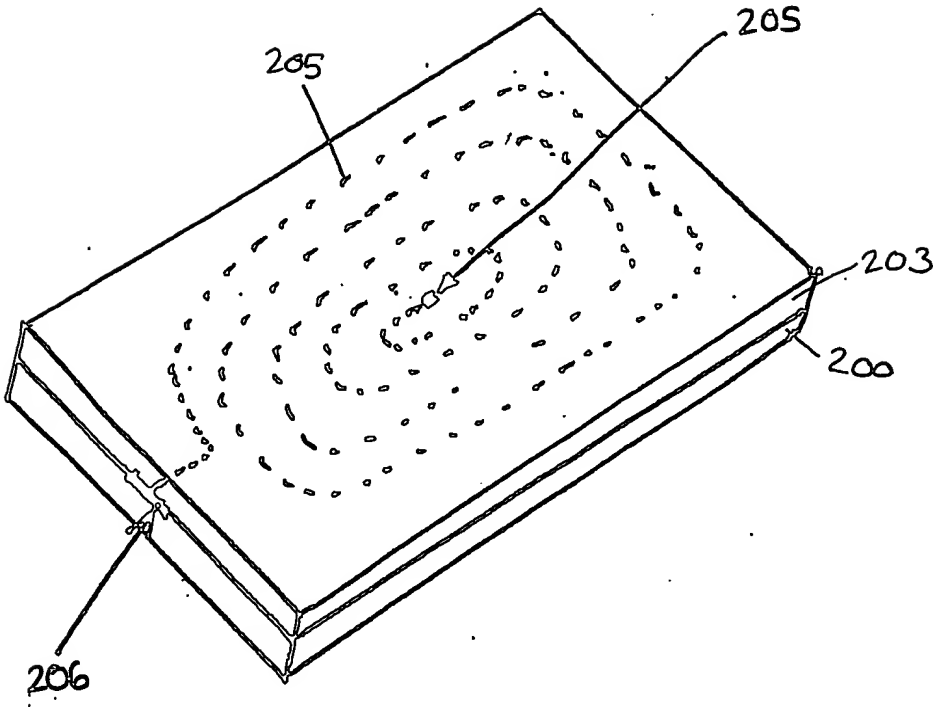

FIG 16

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